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Scientific and Technical Information Center

SEARCH REQUEST FORM

Requester's Full Name: MARK BERCH Examiner #: 59193 Date: 1/24/06

Art Unit: 1624 Phone Number: 2-0663 Serial Number: 10809867

Location (Bldg/Room#): 5C01 (Mailbox #): 5C18 Results Format Preferred (circle): PAPER DISK

****

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: _____

Inventors (please provide full names): _____

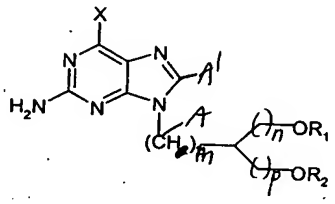
_____

Earliest Priority Date: _____

Search Topic:

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*



A, A' = H / CH_3

X = H or $-S-C$ (↑ ring)

m = 1-4

R, n = 1-3

R_1 / R_2 = H / Si / $\overset{O}{\overset{\|}{C}}$

****

STAFF USE ONLY

Searcher: EJ

Searcher Phone #: _____

Searcher Location: _____

Date Searcher Picked Up: _____

Date Completed: 2-3-06

Searcher Prep & Review Time: _____

Online Time: _____

Type of Search

_____ NA Sequence (#)

_____ AA Sequence (#)

_____ Structure (#)

_____ Bibliographic

_____ Litigation

_____ Fulltext

_____ Other

Vendors and cost where applicable

_____ STN _____ Dialog

_____ Questel/Orbit _____ Lexis/Nexis

_____ Westlaw _____ WWW/Internet

____ In-house sequence systems

____ Commercial ____ Oligomer ____ Score/Length

____ Interference ____ SPDI ____ Encode/Transl

_____ Other (specify)

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=> d his


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L1              STR

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L3           588 S L1 FUL
                 SAV L3 BER967/A

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L14               STR L9
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L16               STR L14
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L22            0 S L19

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L24            5 S L18
L25          481 S L19

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L28            0 S L26 SSS FUL SUB=L3
L29            1 S 104227-87-4
L30          106 S L19 NOT L29

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L31           58 S L30
L32            9 S L23 OR L24
L33           54 S L31 NOT L32
L34           52 S L33 AND (1840-2004/PY OR 1840-2004/PRY)

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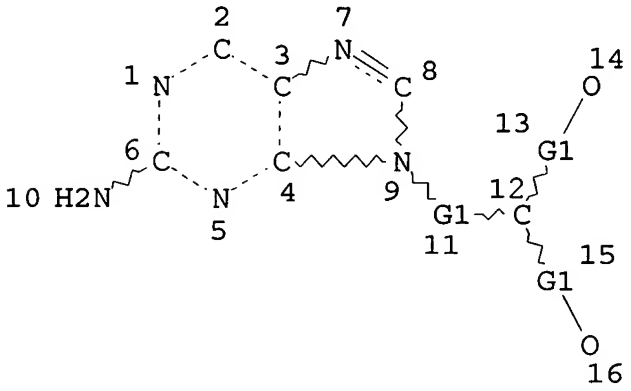


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REP G1=(1-5) C
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DEFAULT ECLEVEL IS LIMITED
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STEREO ATTRIBUTES: NONE
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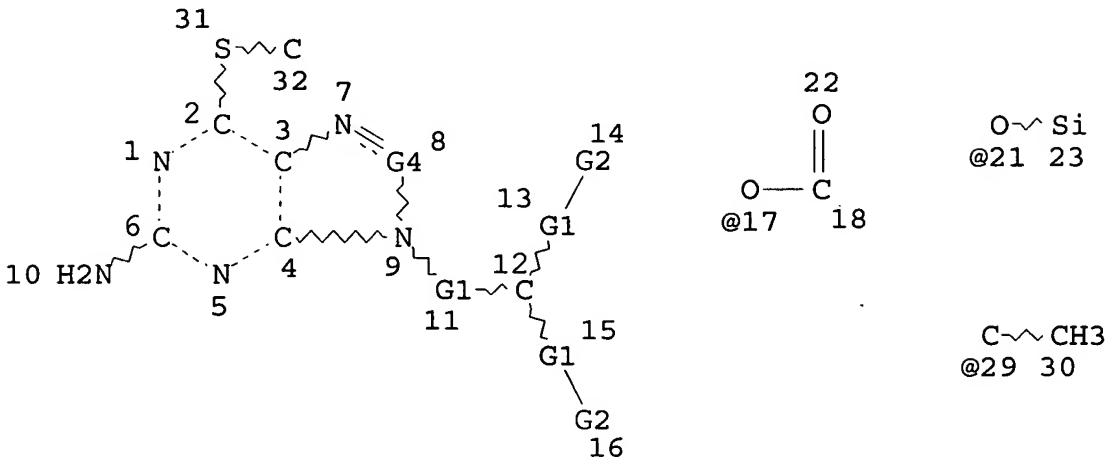

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STEREO ATTRIBUTES: NONE
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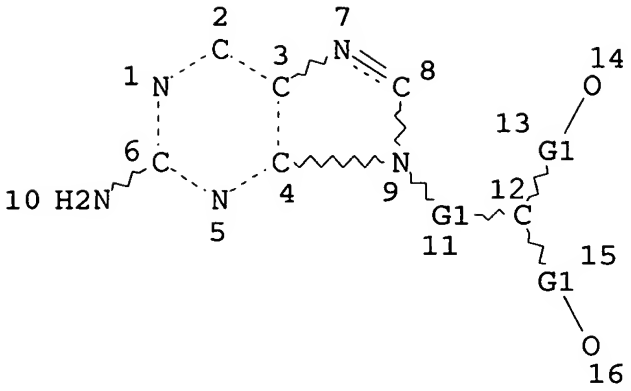

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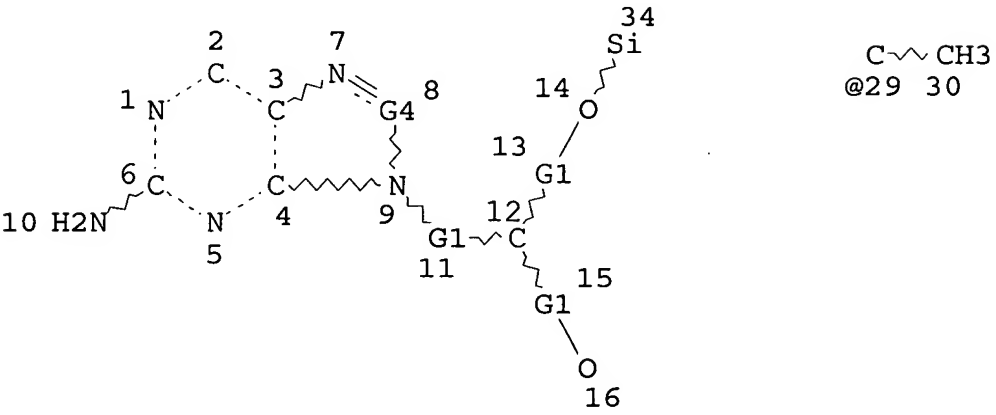

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DEFAULT ECLEVEL IS LIMITED

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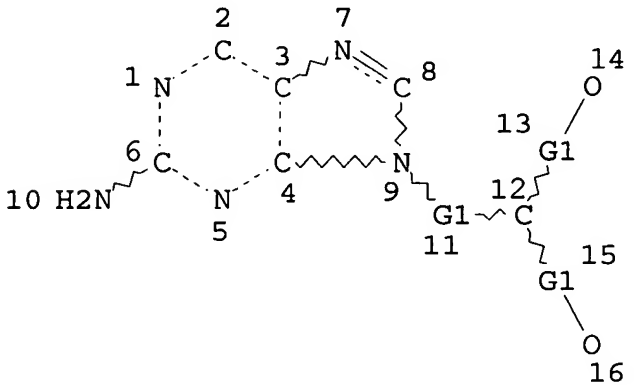

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DEFAULT MLEVEL IS ATOM
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GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 16

STEREO ATTRIBUTES: NONE
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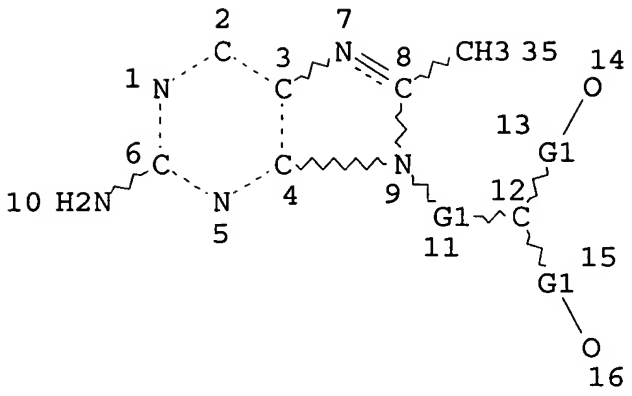

REP G1=(1-5) CH
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 17

STEREO ATTRIBUTES: NONE
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SEARCH TIME: 00.00.01

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FILE 'ZCAPLUS' ENTERED AT 15:49:59 ON 03 FEB 2006
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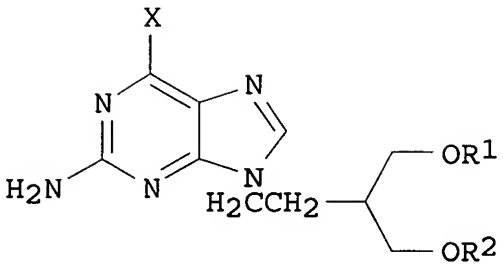
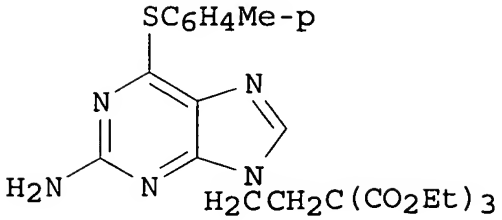
=> d l32 1-9 cbib abs hitstr hitrn

L32 ANSWER 1 OF 9 ZCAPLUS COPYRIGHT 2006 ACS on STN
2005:1050936 Document No. 143:346986 An improved process for the preparation of purines. Joshi, Ramesh Anna; Joshi, Rohini Ramesh; Patil, Pratap Subhashrao; Wakchaure, Vijay Naryan; Gurjar, Mukund Keshav (India). U.S. Pat. Appl. Publ. US 2005215787 A1 20050929, 8 pp. (English). CODEN: USXXCO. APPLICATION: US 2004-809967 20040326.

GI



I



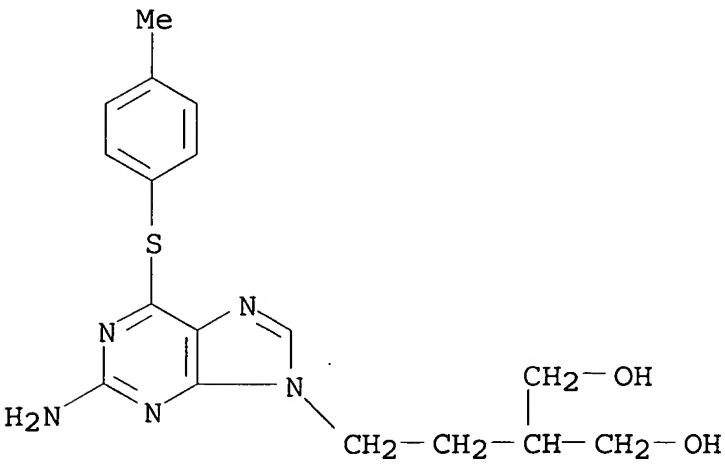
II

AB The purines I (X = H, thioaryl; R1 and R2 = H, acetyl) were prepd. in an improved process. Thus, 2-amino-6-chloropurine was treated with p-thiocresol followed by alkylation with 3-bromopropane-1,1,1-tricarboxylate to give adduct II, which was treated with MeONa in MeOH followed by NaBH4 redn, acetylation and desulfurization using a Ni catalyst to give I (R1 = R2 = Ac; X = H).

IT **865538-73-4P 865538-74-5P**
(improved process for prepn. of purines)

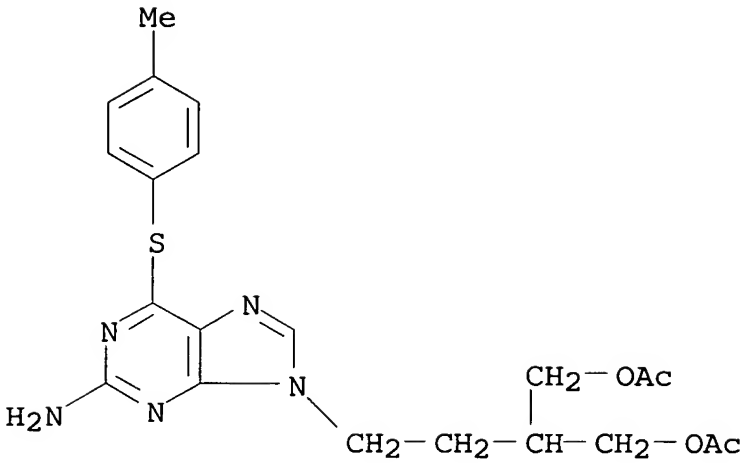
RN 865538-73-4 ZCAPLUS

CN 1,3-Propanediol, 2-[2-[2-amino-6-[(4-methylphenyl)thio]-9H-purin-9-yl]ethyl]- (9CI) (CA INDEX NAME)



RN 865538-74-5 ZCAPLUS

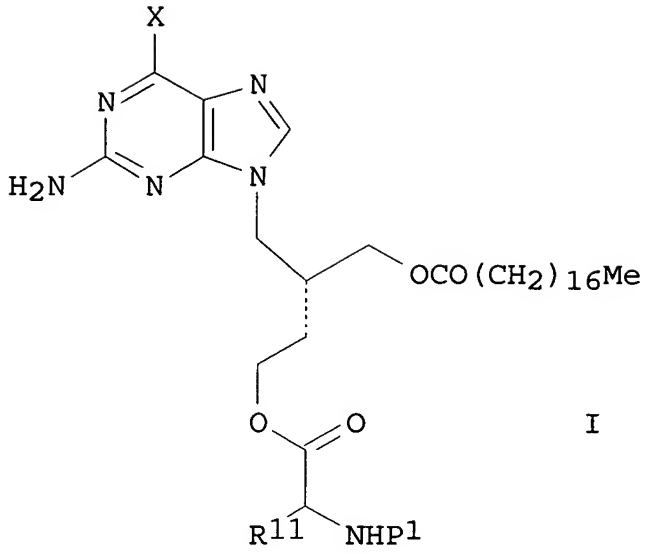
CN 1,3-Propanediol, 2-[2-[2-amino-6-[(4-methylphenyl)thio]-9H-purin-9-yl]ethyl]-, diacetate (ester) (9CI) (CA INDEX NAME)



IT **865538-73-4P 865538-74-5P**
(improved process for prepn. of purines)

L32 ANSWER 2 OF 9 ZCAPLUS COPYRIGHT 2006 ACS on STN
2001:91538 Document No. 134:147852 Synthesis of acyclic nucleoside derivatives. Leanna, M. Robert; Hannick, Steven M.; Rasmussen, Michael; Tien, Jien-Heh J.; Bhagavatula, Lakshmi; Singam, Pulla Reddy; Gates, Bradley D.; Kolaczkowski, Lawrence; Patel, Ramesh R.; Wayne, Greg; Lannoye, Greg; Zhang, Weijiang; Tian, Zhenping; Lukin, Kirill A.; Narayanan, Bikshandarkoil A.; Riley, David A.; Morton, Howard; Chang, Sou-Jen; Curty, Cynthia B.; Plata, Daniel; Bellettini, John; Shelat, Bhadra; Spitz, Tiffany; Yang, Cheng-Xi (Mediver AB, Swed.). U.S. US 6184376 B1 20010206, 41 pp., Cont.-in-part of U.S. Ser. No. 20,231, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1998-130214 19980806. PRIORITY: US 1997-PV37517 19970210; US 1997-PV55153 19970808; US 1998-20231 19980206.

GI



I

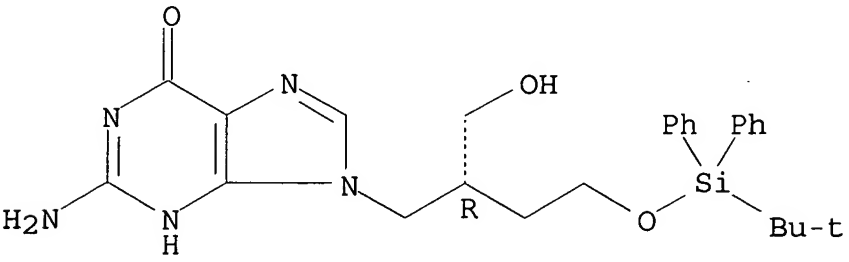
AB Acyclic nucleoside derivs., including amino acid derivs. I (X = Br or iodo; R11 = iso-Pr or isobutyl; P1 is an N-protecting group), were prepd. for use as pharmaceuticals. Thus, (R)-9-[2-(stearoyloxymethyl)-4-(L-valyloxy)butyl]guanine monohydrochloride was prepd. from 9-[4-hydroxy-2-(hydroxymethyl)butyl]guanine (H2G) and shown to have antiviral activity significantly greater than that of acyclovir.

IT **195157-16-5P 195157-17-6P 324016-51-5P**
(synthesis of acyclic nucleoside derivs.)

RN 195157-16-5 ZCAPLUS

CN 6H-Purin-6-one, 2-amino-9-[(2R)-4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2-(hydroxymethyl)butyl]-1,9-dihydro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

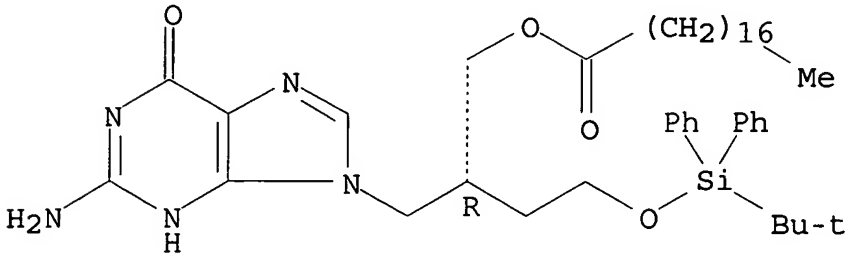


RN 195157-17-6 ZCAPLUS

CN Octadecanoic acid, (2R)-2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-

yl)methyl]-4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]butyl ester (9CI) (CA INDEX NAME)

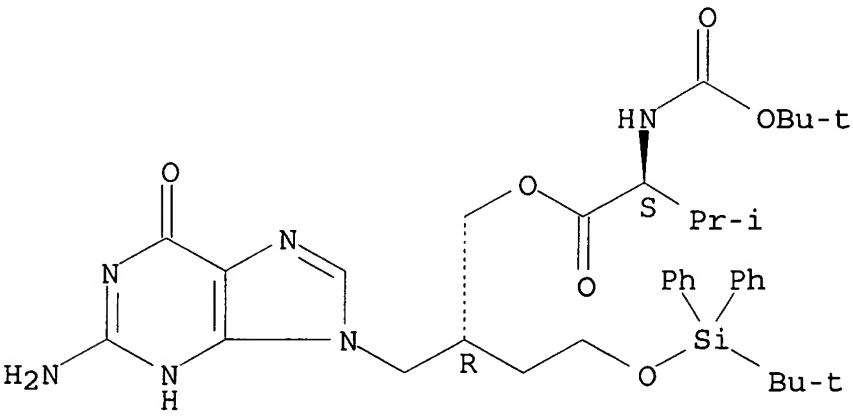
Absolute stereochemistry.



RN 324016-51-5 ZCAPLUS

CN 5,10-Dioxa-2-aza-11-silatridecanoic acid, 7-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methyl]-12,12-dimethyl-3-(1-methylethyl)-4-oxo-11,11-diphenyl-, 1,1-dimethylethyl ester, (3S,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



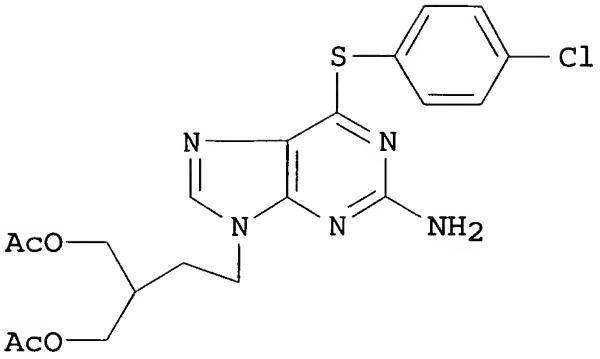
IT **195157-16-5P 195157-17-6P 324016-51-5P**
(synthesis of acyclic nucleoside derivs.)

L32 ANSWER 3 OF 9 ZCAPLUS COPYRIGHT 2006 ACS on STN

1999:270561 Document No. 131:5235 Convenient syntheses of 9-[4-hydroxy-3-(hydroxymethyl)butyl]guanine (penciclovir) and 9-[4-acetoxy-3-(acetoxymethyl)butyl]-2-amino-9H-purine (famciclovir). Brand, Briony; Reese, Colin B.; Song, Quanlai; Visintin, Cristina (Department of Chemistry, King's College London, London, WC2R 2LS, UK). Tetrahedron, 55(16), 5239-5252 (English) 1999. CODEN: TETRAB. ISSN: 0040-4020. Publisher: Elsevier Science

Ltd..

GI



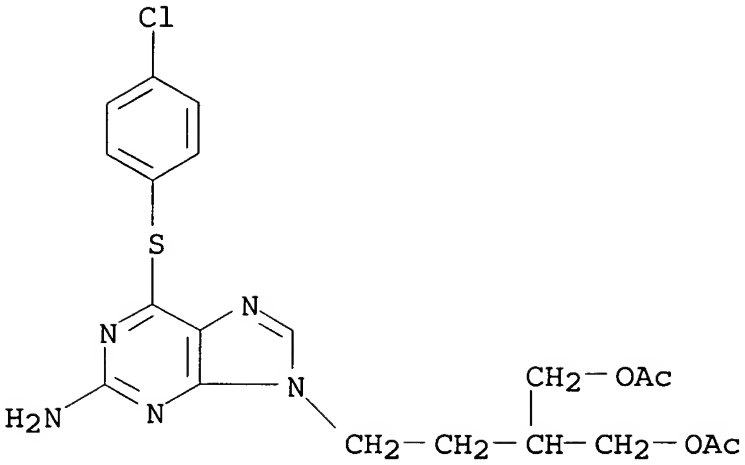
III

AB Guanine was converted, in a one pot reaction, to 2-amino-6-[(4-chlorophenyl)thio]purine (I) in 88% isolated yield. 4-Acetoxy-3-(acetoxymethyl)butanol (II) was prepd. from 2-chloroethanol in five steps and in 46% overall yield. The mesylate ester of II reacted with I in the presence of potassium carbonate with a high degree of regioselectivity (89%) to give the N-9 alkylated product (III), which was isolated in 80% yield. Acidic hydrolysis of III gave penciclovir in virtually quant. yield. Penciclovir and famciclovir were prepd. from I in four and five steps, resp., by procedures involving initial alkylation with 1,2-dibromoethane. The overall yields were 65 and ca. 60%, resp.

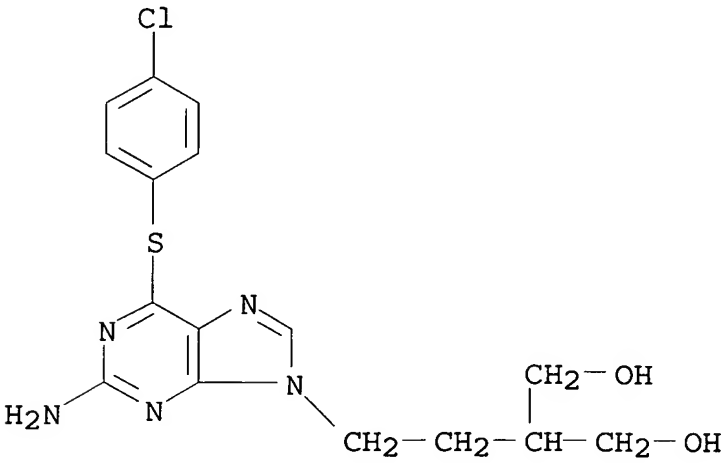
IT **225111-66-0P 225111-70-6P**
(convenient prepns. of penciclovir and famciclovir)

RN 225111-66-0 ZCAPLUS

CN 1,3-Propanediol, 2-[2-[2-amino-6-[(4-chlorophenyl)thio]-9H-purin-9-yl]ethyl]-, diacetate (ester) (9CI) (CA INDEX NAME)



RN 225111-70-6 ZCAPLUS
CN 1,3-Propanediol, 2-[2-[2-amino-6-[(4-chlorophenyl)thio]-9H-purin-9-yl]ethyl]- (9CI) (CA INDEX NAME)

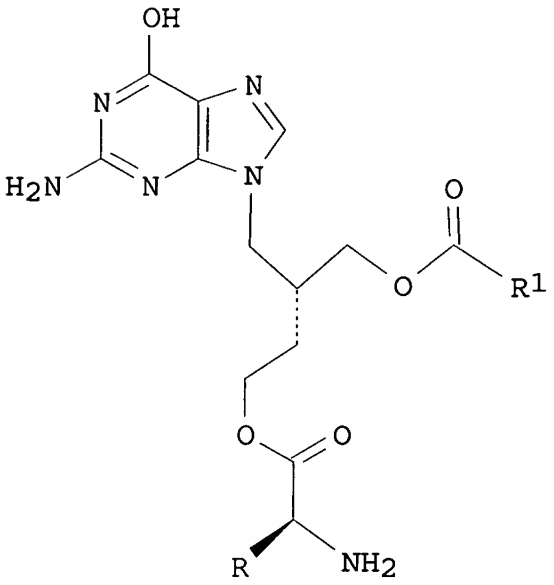


IT **225111-66-0P 225111-70-6P**
(convenient prepns. of penciclovir and famciclovir)

L32 ANSWER 4 OF 9 ZCAPLUS COPYRIGHT 2006 ACS on STN
1998:550409 Document No. 129:175918 Synthesis and bioavailability of acyclic nucleosides as antiviral agents. Leanna, M. Robert; Hannick, Steven M.; Rasmussen, Michael; Tien, Jien-Heh J.; Bhagavatula, Lakshmi; Singam, Pulla Reddy; Gates, Bradley D.; Kolaczkowski, Lawrence; Patel, Ramesh R.; Wayne, Greg; Lannoye, Greg; Zhang, Weijiang; Tian, Zhenping; Lukin, Kirill L.; Narayanan,

Bikshandarkor A.; Riley, David A.; Morton, Howard; Chang, Sou-jen (Abbott Laboratories, USA). PCT Int. Appl. WO 9834917 A2 19980813, 109 pp. DESIGNATED STATES: W: CA, JP, MX; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US2439 19980206. PRIORITY: US 1997-798216 19970210; US 1997-37517 19970210; US 1997-908754 19970808.

GI



I

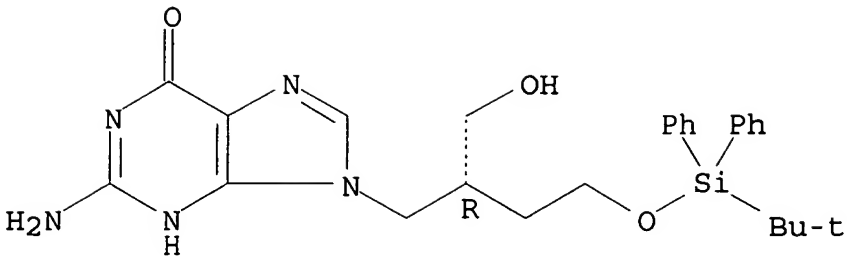
AB Acyclic nucleosides I (R = iPr, iBu; R1 = C3-C21 satd. or mono-unsatd. alkyl) were prepd. as virucides. Thus, (R)-9-[2-(stearoyloxymethyl)-4-(L-valyloxy)butyl]guanine was prepd. and tested for its bioavailability (56%) in rats and monkeys and for its HSV-1 activity in mice.

IT **195157-16-5P 195157-17-6P**
(synthesis and bioavailability of acyclic nucleosides as antiviral agents)

RN 195157-16-5 ZCAPLUS

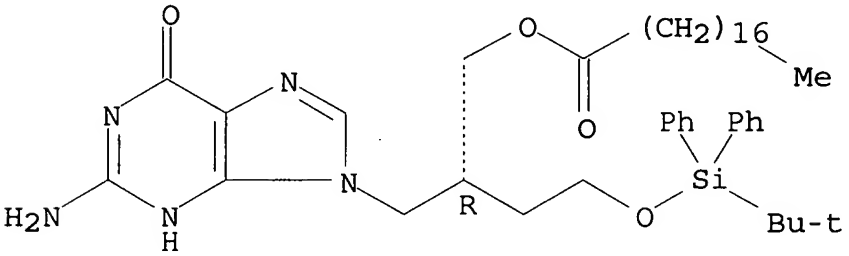
CN 6H-Purin-6-one, 2-amino-9-[(2R)-4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2-(hydroxymethyl)butyl]-1,9-dihydro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 195157-17-6 ZCAPLUS
CN Octadecanoic acid, (2R)-2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methyl]-4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]butyl ester (9CI) (CA INDEX NAME)

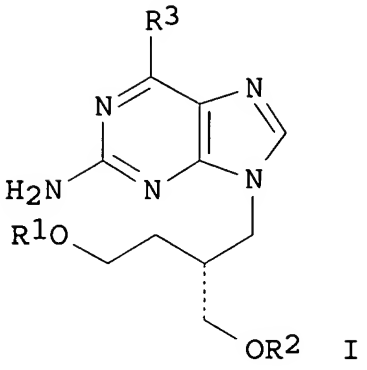
Absolute stereochemistry.



IT **195157-16-5P 195157-17-6P**
(synthesis and bioavailability of acyclic nucleosides as antiviral agents)

L32 ANSWER 5 OF 9 ZCAPLUS COPYRIGHT 2006 ACS on STN
1997:568117 Document No. 127:234606 Preparation of acyclic nucleoside esters with amino acids and fatty acids as antiviral agents. Engelhardt, Per; Hogberg, Marita; Zhou, Xiao-xiong; Lindborg, Bjorn; Johansson, Nils Gunnar (Medivir AB, Swed.). PCT Int. Appl. WO 9730052 A1 19970821, 74 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-SE242 19970214. PRIORITY: SE 1996-613 19960216; SE 1996-614 19960216.

GI



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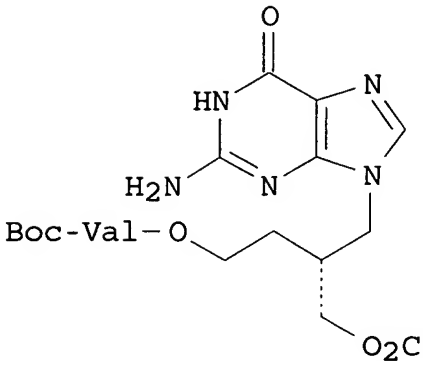


II

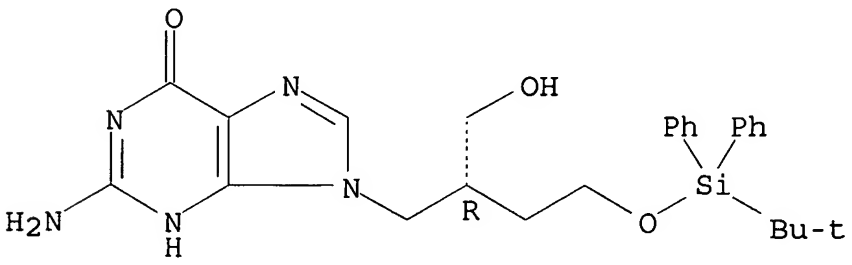
AB Title compds. I (R1 = H-Val, H-Ile, R2 = optionally substituted, satd. or monounsatd. CO-C3-21-alkyl; R1 = optionally substituted, satd. or monounsatd. CO-C3-21-alkyl, R2 = H-Val, H-Ile; R3 = H, OH) and pharmaceutically acceptable salts thereof were prepd. as antivirals with enhanced bioavailability against herpes and retroviral infections. Thus, sequential esterification of (R)-9-(4-hydroxy-2-hydroxymethylbutyl)guanine with Boc-Val-OH (Boc = Me3CO2C) and stearoyl chloride, followed by deprotection with CF3CO2H gave acyclic nucleoside diester II as its bis(trifluoroacetate) salt. Bioavilabilities and antiviral activities of II and related prepd. compds. against herpes simplex virus-1 are given.

IT **195157-16-5P 195157-17-6P**
(prepn. of acyclic nucleoside esters with amino acids and fatty acids as antiviral agents)

RN 195157-16-5 ZCAPLUS

CN 6H-Purin-6-one, 2-amino-9-[(2R)-4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2-(hydroxymethyl)butyl]-1,9-dihydro- (9CI) (CA INDEX NAME)

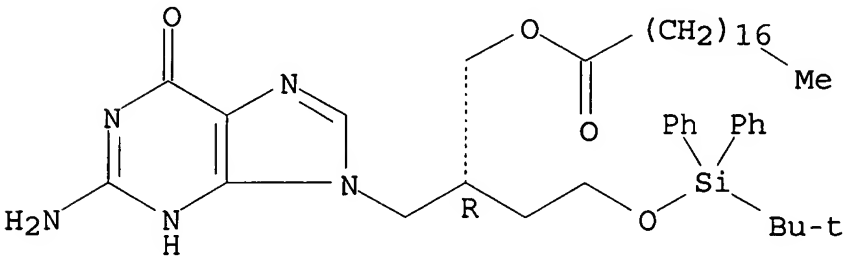
Absolute stereochemistry.



RN 195157-17-6 ZCAPLUS

CN Octadecanoic acid, (2R)-2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methyl]-4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]butyl ester (9CI) (CA INDEX NAME)

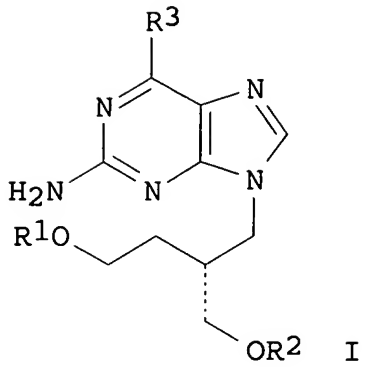
Absolute stereochemistry.



IT **195157-16-5P 195157-17-6P**
(prepn. of acyclic nucleoside esters with amino acids and fatty acids as antiviral agents)

L32 ANSWER 6 OF 9 ZCAPLUS COPYRIGHT 2006 ACS on STN
1997:568115 Document No. 127:234605 Preparation of acyclic nucleoside esters with amino acids and fatty acids as antiviral agents. Engelhardt, Per; Hogberg, Marita; Zhou, Xiao-xiong; Lindborg, Bjorn; Johansson, Nils Gunnar (Medivir AB, Swed.). PCT Int. Appl. WO 9730051 A1 19970821, 79 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-SE241 19970214. PRIORITY: SE 1996-613 19960216; SE 1996-614 19960216.

GI



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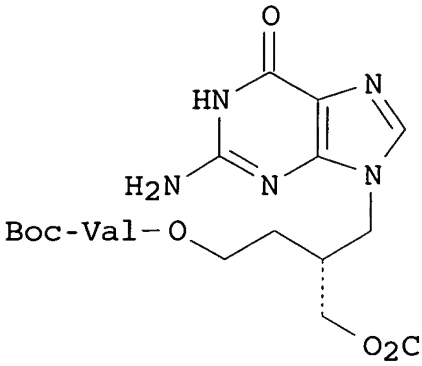


II

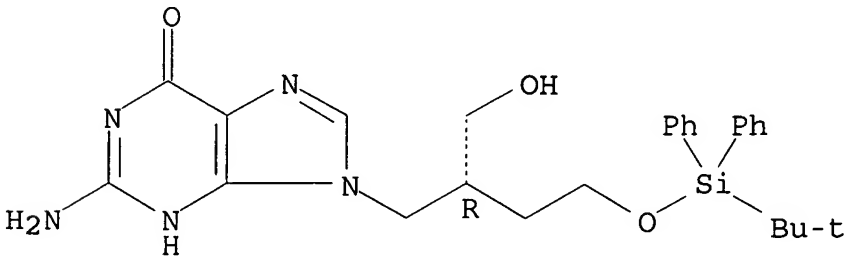
AB Title compds. I (R1 = H-Val, H-Ile, R2 = optionally substituted, satd. or monounsatd. CO-C3-21-alkyl; R1 = optionally substituted, satd. or monounsatd. CO-C3-21-alkyl, R2 = H-Val, H-Ile; R3 = H, OH) and pharmaceutically acceptable salts thereof have utility as enhanced bioavailability antivirals against herpes and retroviral infections. Thus, sequential esterification of (R)-9-(4-hydroxy-2-hydroxymethylbutyl)guanine with Boc-Val-OH (Boc = Me3CO2C) and stearoyl chloride, followed by deprotection with CF3CO2H gave acyclic nucleoside diester II as its bis(trifluoroacetate) salt. Bioavilabilities and antiviral activities of II and related prepd. compds. are given.

IT **195157-16-5P 195157-17-6P**
(prepn. of acyclic nucleoside esters with amino acids and fatty acids as antiviral agents)

RN 195157-16-5 ZCAPLUS

CN 6H-Purin-6-one, 2-amino-9-[(2R)-4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2-(hydroxymethyl)butyl]-1,9-dihydro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

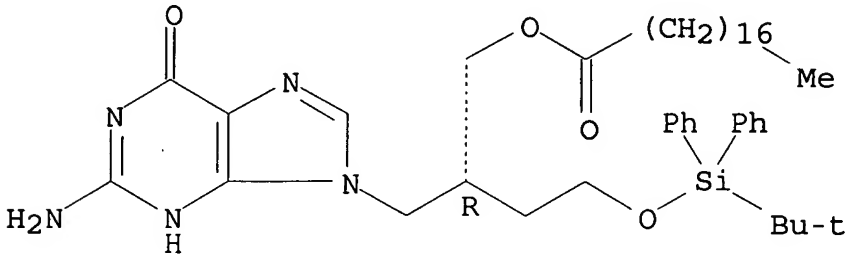


RN 195157-17-6 ZCAPLUS

CN Octadecanoic acid, (2R)-2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-

yl)methyl]-4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]butyl ester (9CI) (CA INDEX NAME)

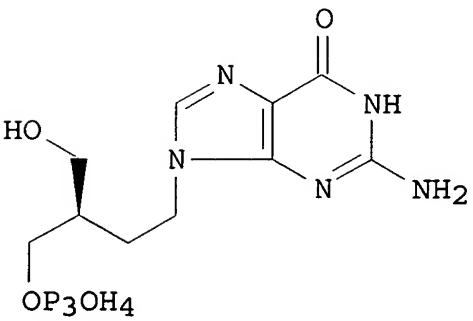
Absolute stereochemistry.



IT **195157-16-5P 195157-17-6P**
(prepn. of acyclic nucleoside esters with amino acids and fatty acids as antiviral agents)

L32 ANSWER 7 OF 9 ZCAPLUS COPYRIGHT 2006 ACS on STN
1997:34050 Document No. 126:60295 Preparation of (R)-penciclovir triphosphate as virucide. Vere, Hodge Richard Anthony; Schinazi, Raymond F. (Smithkline Beecham Plc, UK). PCT Int. Appl. WO 9633720 A1 19961031, 32 pp. DESIGNATED STATES: W: JP, US; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-EP1706 19960423. PRIORITY: GB 1995-8237 19950424; GB 1996-4909 19960308.

GI



I

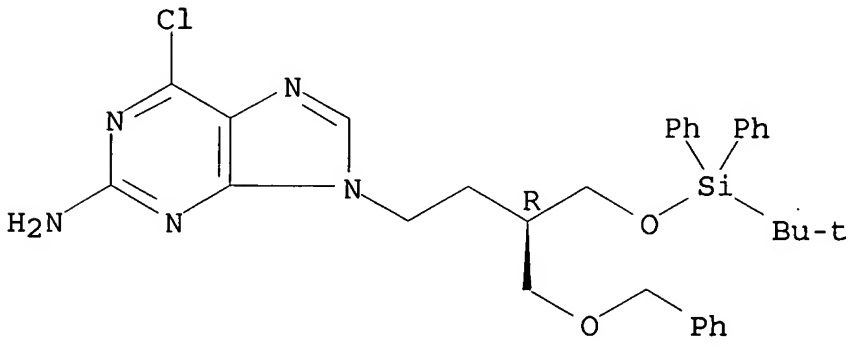
AB Acyclic nucleotides, e.g. I, were prepd. as virucides (no data).

IT **185031-36-1P 185031-45-2P**
(prepn. of (R)-penciclovir triphosphate as virucide)

RN 185031-36-1 ZCAPLUS

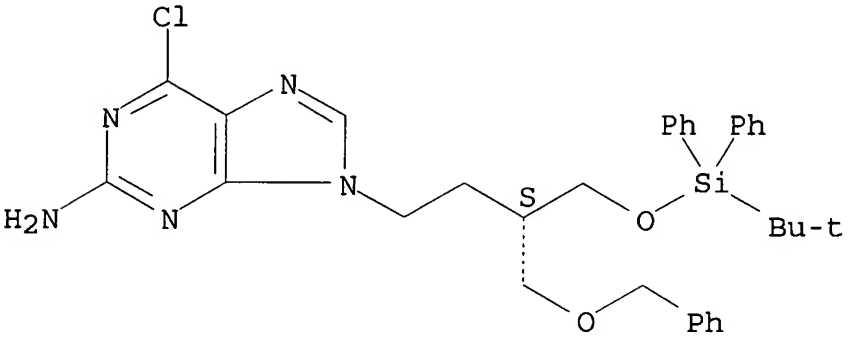
CN 9H-Purin-2-amine, 6-chloro-9-[3-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-4-(phenylmethoxy)butyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



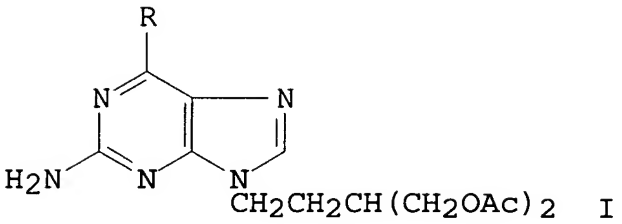
RN 185031-45-2 ZCAPLUS
CN 9H-Purin-2-amine, 6-chloro-9-[3-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-4-(phenylmethoxy)butyl]-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **185031-36-1P 185031-45-2P**
(prepn. of (R)-penciclovir triphosphate as virucide)

L32 ANSWER 8 OF 9 ZCAPLUS COPYRIGHT 2006 ACS on STN
1991:43461 Document No. 114:43461 The effect of the C-6 substituent on the regioselectivity of N-alkylation of 2-aminopurines. Geen, Graham R.; Grinter, Trevor J.; Kincey, Peter M.; Jarvest, Richard L. (Biosci. Res. Cent., Beecham Pharm. Res. Div., Epsom/Surrey, KT18 5XQ, UK). Tetrahedron, 46(19), 6903-14 (English) 1990. CODEN: TETRAB. ISSN: 0040-4020.
GI



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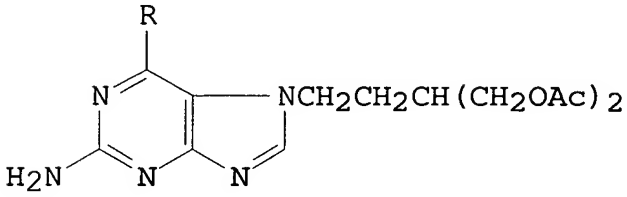


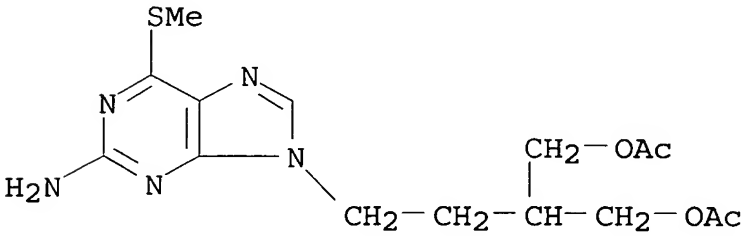
II

AB 6-Substituted 2-aminopurines were N-alkylated with 2-actoxymethyl-4-iodobutyl acetate. The ratio of N-9 (I) to N-7 (II, R = H, OMe, SMe, F, Cl, Br, iodo, Me, Et, CF3, CHMe2) varied from 1.8:1 to 25:1. The log of this ratio correlated with a combination of resonance and lipopohilicity parameters of the C-6 substituent of the purine.

IT **131266-16-5P**
(prepn. of)

RN 131266-16-5 ZCAPLUS

CN 1,3-Propanediol, 2-[2-[2-amino-6-(methylthio)-9H-purin-9-yl]ethyl]-, diacetate (ester) (9CI) (CA INDEX NAME)



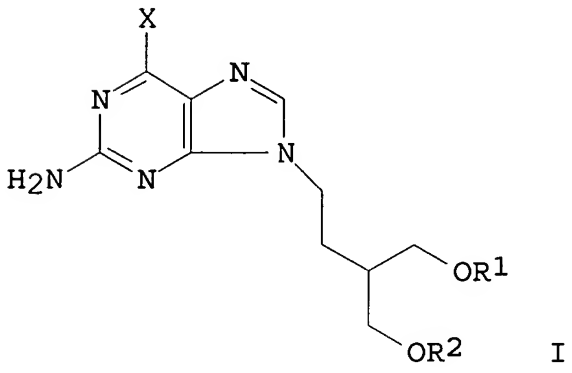
IT **131266-16-5P**
(prepn. of)

L32 ANSWER 9 OF 9 ZCAPLUS COPYRIGHT 2006 ACS on STN

1990:440345 Document No. 113:40345 Preparation of purine derivatives

as virucides. Grinter, Trevor John; Kincey, Peter Markham (Beecham Group PLC, UK). Eur. Pat. Appl. EP 352953 A2 19900131, 19 pp. DESIGNATED STATES: R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1989-307271 19890718. PRIORITY: GB 1988-17607 19880723.

GI



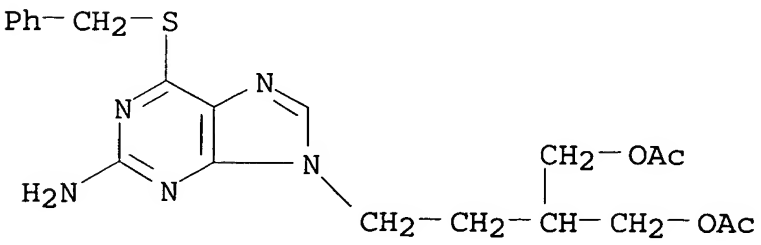
I

AB The title compds. (I; X = H, OH; R1, R2 = H, R3CO; R3 = Ph, alkyl), useful as virucides (no data), were prepd. by N-9 alkylation of aminopurines 6-substituted by a leaving group, followed by hydrolysis/hydrogenolysis. Thus, (AcOCH2)2CHCH2CH2I, 2-amino-6-iodopurine, and K2CO3 were stirred 18 h in DMF to give 79.4% I (X = I, R1 = R2 = Ac). The latter was hydrogenated in EtOH over Pd/C to give I (X = H; R1, R2 unchanged).

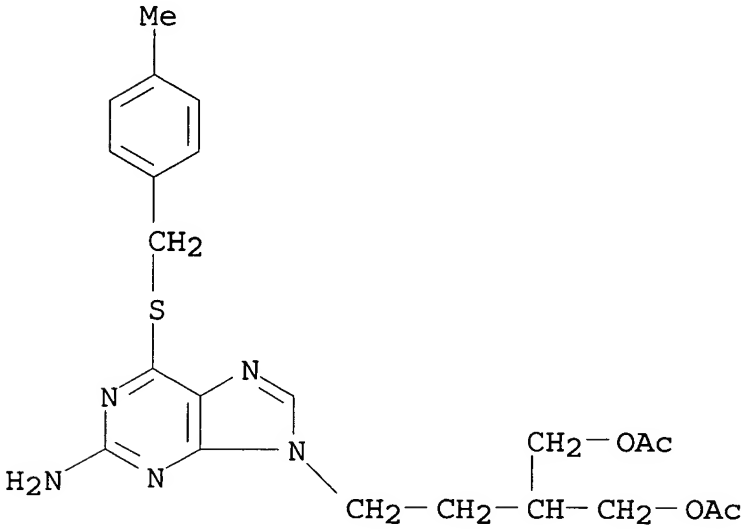
IT **128139-28-6P 128139-29-7P 128139-30-0P 128139-36-6P**
(prepn. of, as virucide intermediate)

RN 128139-28-6 ZCAPLUS

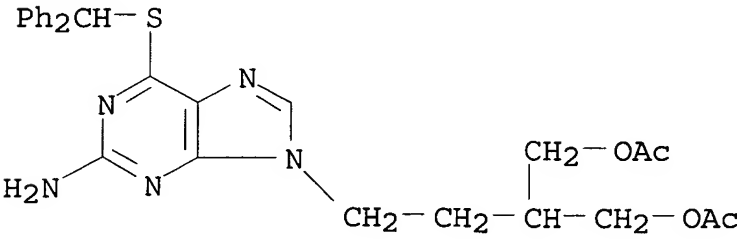
CN 1,3-Propanediol, 2-[2-[2-amino-6-[(phenylmethyl)thio]-9H-purin-9-yl]ethyl]-, diacetate (ester) (9CI) (CA INDEX NAME)



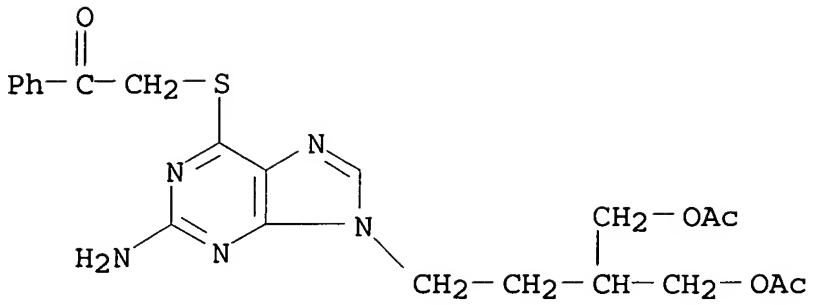
RN 128139-29-7 ZCAPLUS
CN 1,3-Propanediol, 2-[2-[2-amino-6-[[(4-methylphenyl)methyl]thio]-9H-purin-9-yl]ethyl]-, diacetate (ester) (9CI) (CA INDEX NAME)



RN 128139-30-0 ZCAPLUS
CN 1,3-Propanediol, 2-[2-[2-amino-6-[(diphenylmethyl)thio]-9H-purin-9-yl]ethyl]-, diacetate (ester) (9CI) (CA INDEX NAME)



RN 128139-36-6 ZCAPLUS
CN Ethanone, 2-[[9-[4-(acetyloxy)-3-[(acetyloxy)methyl]butyl]-2-amino-9H-purin-6-yl]thio]-1-phenyl- (9CI) (CA INDEX NAME)



IT **128139-28-6P 128139-29-7P 128139-30-0P**
128139-36-6P
(prepn. of, as virucide intermediate)

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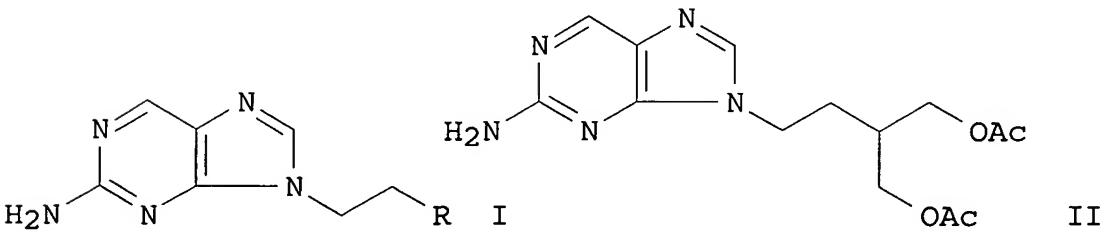
L34 ANSWER 1 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
2004:1124561 Document No. 142:56088 Process for the preparation of 2-amino-9-(2-substituted-ethyl)purines and 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine (famciclovir). Lee, Byoung-Suk; Shin, Sang-Hoon; Park, Jong-Sik (Kyungdong Pharm. Co., Ltd., S. Korea). PCT Int. Appl. WO 2004110343 A2 **20041223**, 26 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-KR1405 20040612. PRIORITY: KR 2003-38417 20030613.

GI

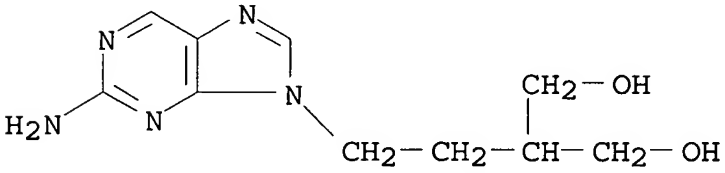


AB The present invention relates to a process for prepg. of 2-amino-9-(2-substituted-ethyl)purines, such as I [R = OH, OSO2Me, OSO2C6H4-4-Me, halogen], and an effective method for prepg. 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurin (famciclovir) (II). The inventive method for the prepn. of II comprised the steps of halogenating alc. I (R = OH) to give 2-amino-9-(2-haloethyl)purine I (R = halogen), reacting the halogenated compd. with di-Et malonate, redn. of the dicarboxylate, and diacetylation of the resulting diol. The inventive prepn. method allows II, a purine deriv. drug with effective antiviral activity, to be prepd. in a high selectivity of 100% in a pure form by using the intermediate purines I. In addn., the inventive method allows the utilization of relatively mild reaction conditions, and thus, has high industrial process efficiency.

IT **104227-86-3P**
(process for prepn. of 2-amino-9-(2-substituted-ethyl)purines and 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine (famciclovir))

RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



IT **104227-86-3P**
(process for prepn. of 2-amino-9-(2-substituted-ethyl)purines and 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine (famciclovir))

L34 ANSWER 2 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

2004:996181 Document No. 141:411197 Process for the preparation of famciclovir. Shamai, Genny; Antebi, Shlomo; Ioffe, David; Dolitzky, Ben-Zion; Kauffmann, Batia (Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.). PCT Int. Appl. WO 2004099208 A1 **20041118**, 19 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG,

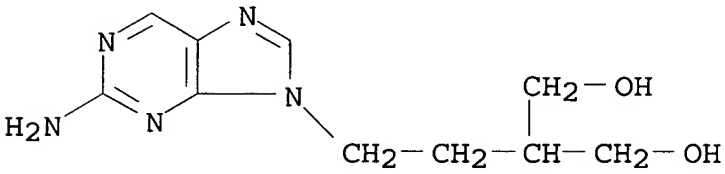
CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US13427 20040430. PRIORITY: US 2003-PV466705 20030430; US 2003-PV488268 20030716.

AB The invention provides processes for making famciclovir with low levels of undesirable byproducts. The present invention discloses a process comprises reacting acetic acid 2-acetoxymethyl-4-(5-amino-7-chloro-imidazo[4,5-b]pyridin-3-yl)butyl ester (I) in the presence of a palladium on charcoal catalyst in a C1-C6 alkyl acetate and ammonium formate. The present invention further discloses a process comprises reacting I in the presence of a palladium on charcoal catalyst in a mixt. of a C1-C6 alkyl acetate, a C1-C4 alc. and ammonium formate.

IT **104227-86-3P 104227-88-5P**
(prepn. of famciclovir)

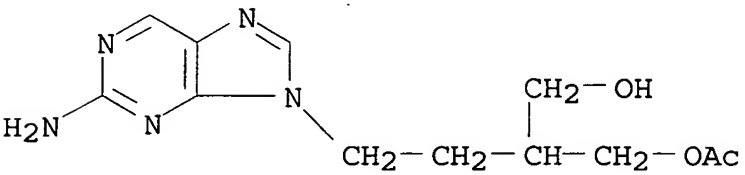
RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



RN 104227-88-5 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monoacetate (ester) (9CI) (CA INDEX NAME)



IT **104227-86-3P 104227-88-5P**
(prepn. of famciclovir)

L34 ANSWER 3 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

2004:991637 Document No. 143:253590 Novel synthesis technology for Famciclovir. Jin, Yicui (College of Pharmacy and Life Science, Nanjing University of Technology, Nanjing, Jiangsu Province, 210019, Peop. Rep. China). Jingxi Huagong Zhongjianti, 34(4), 39-41 (Chinese) **2004.** CODEN: JHZIAR. ISSN: 1009-9212.

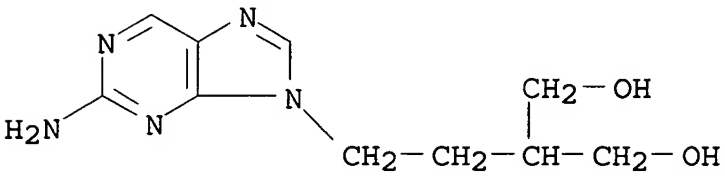
Publisher: Jingxi Huagong Zhongjianti Zazhishe.

AB The reaction time, temp., reagents were studied to raise the overall yield from <21% to .apprx.30%. The purity was >99%.

IT **104227-86-3P**
(synthesis of Famciclovir antivirus drug)

RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



IT **104227-86-3P**
(synthesis of Famciclovir antivirus drug)

L34 ANSWER 4 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

2004:734533 Document No. 141:366075 Regioselective functionalization of guanine: Simple and practical synthesis of 7- and 9-alkylated guanines starting from guanosine. Kalayanov, Genadiy; Jaksa, Suzana; Scarcia, Tommaso; Kobe, Joze (National Institute of Chemistry, Ljubljana, 1115, Slovenia). Synthesis (12), 2026-2034 (English) **2004.** CODEN: SYNTBF. ISSN: 0039-7881. OTHER SOURCES: CASREACT 141:366075. Publisher: Georg Thieme Verlag.

GI

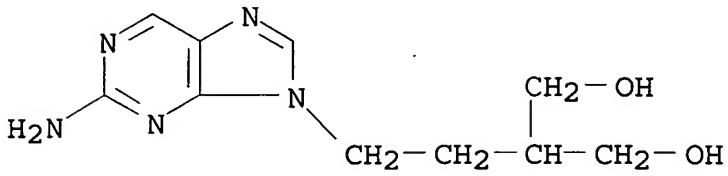
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Reaction of N2-acetyl-9- and/or -7-benzylated guanines with selected alkylating agents in 1-methyl-2-pyrrolidone at 120 .degree.C yielded the guaninium salts, e.g. I and II. The salts were consequently transformed by phase transfer hydrogenation into N7- and N9-isomers, e.g. III and IV, resp., in a highly regioselective manner. A convenient deoxygenation of both derivs., achieved via the corresponding O6-arenesulfonates, into 2-aminopurine potential prodrugs was also established.

IT **104227-86-3P**
(regioselective functionalization of guanine, simple and practical synthesis of 7- and 9-alkylated guanines starting from guanosine)

RN 104227-86-3 ZCAPLUS

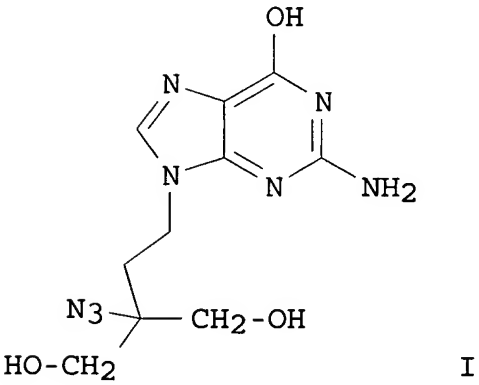
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



IT **104227-86-3P**
(regioselective functionalization of guanine, simple and practical synthesis of 7- and 9-alkylated guanines starting from guanosine)

L34 ANSWER 5 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
2004:274884 Document No. 141:54564 Synthesis and biological evaluation of novel tert-azido or tert-amino substituted penciclovir analogs. Kim, Hea Ok; Baek, Hye Won; Moon, Hyung Ryong; Kim, Dae-Kee; Chun, Moon Woo; Jeong, Lak Shin (Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul, 120-750, S. Korea). Organic & Biomolecular Chemistry, 2(8), 1164-1168 (English) **2004.** CODEN: OBCRAK. ISSN: 1477-0520. OTHER SOURCES: CASREACT 141:54564. Publisher: Royal Society of Chemistry.

GI



I

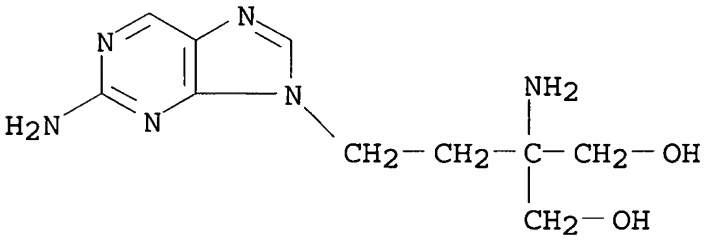
AB Tert-Azido or amino substituted penciclovir analogs, were synthesized for the purpose of improving the efficacy and bioavailability of penciclovir and searching for novel antiviral agents. Among several methods attempted to insert an azido group

into the .alpha.,.beta.-unsatd. ester, only Bronsted acid-catalyzed 1,4-conjugate addn. conditions (NaN3, 75% acetic acid, 80 .degree.C) gave the desired tert-azido product. The synthesized final penciclovir analogs were evaluated in vitro against several viruses such as HIV-1, HSV-1 and 2, poliovirus, VZV, and VSV. I only showed weak antiviral activity against HSV-1 without cytotoxicity. Although the synthesized compds. did not exhibit an excellent antiviral activity, the successful method used in introducing the tert-azido group is expected to be generally utilized for the synthesis of nucleoside analogs with a tert-azido substituent.

IT **705965-02-2P**
(synthesis and in vitro antiviral evaluation of tert-azido or tert-amino substituted penciclovir analogs)

RN 705965-02-2 ZCAPLUS

CN 1,3-Propanediol, 2-amino-2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



IT **705965-02-2P**
(synthesis and in vitro antiviral evaluation of tert-azido or tert-amino substituted penciclovir analogs)

L34 ANSWER 6 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

2004:182880 Document No. 140:235744 Crystalline solid famciclovir forms I, II, III and preparation thereof. Dolitzky, Ben-Zion; Wizel, Shlomit; Reany, Ofer; Shammai, Jenny (Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.). PCT Int. Appl. WO 2004018470 A2 **20040304**, 28 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US26875 20030826. PRIORITY: US 2002-2002/PV40617U 20020826; US 2002-2002/PV422243 20021029.

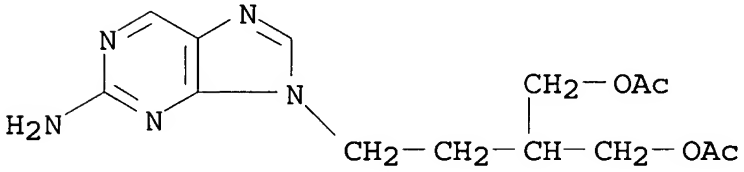
AB The present invention provides novel cryst. solid anhyd. forms of

famciclovir, denominated form I, II, and III, as well as their prepns. thereof by crystn. from org. solvents, and pharmaceutical compns. Thus, famciclovir (a mixt. of cryst. solid famciclovir form I and form II) (3 g) was dissolved in a min. vol. of CH2Cl2 while stirring. If necessary, the mixt. was warmed for a short time until no ppt. was obsd. The soln. was then cooled to room temp. and allowed to stand overnight. If required, the soln. was left to stand for a longer period of time. The crystals (a substantially pure cryst. solid famciclovir form I) were filtered off and dried at 40.degree. under vacuum.

IT **131118-73-5P**, Famciclovir monohydrate
(dehydration; prepn. of cryst. solid famciclovir forms I, II, III by crystn. from org. solvents and/or water)

RN 131118-73-5 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, diacetate (ester), monohydrate (9CI) (CA INDEX NAME)



● H_2O

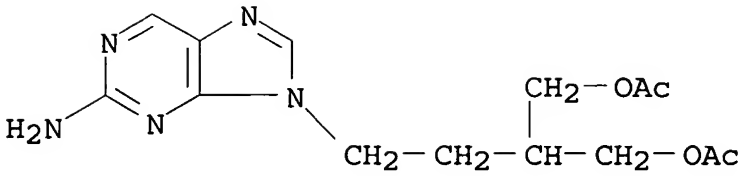
IT **666832-88-8P**, Famciclovir methanol solvate
666832-89-9P, Famciclovir ethanol solvate
(prepn. of cryst. solid famciclovir forms I, II, III by crystn. from org. solvents and/or water)

RN 666832-88-8 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, diacetate (ester), compd. with methanol (1:1) (9CI) (CA INDEX NAME)

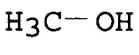
CM 1

CRN 104227-87-4
CMF C14 H19 N5 O4



CM 2

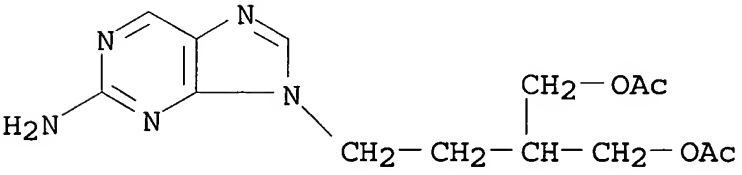
CRN 67-56-1
CMF C H4 O



RN 666832-89-9 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, diacetate (ester), compd. with ethanol (1:1) (9CI) (CA INDEX NAME)

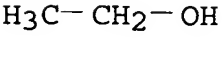
CM 1

CRN 104227-87-4
CMF C14 H19 N5 O4



CM 2

CRN 64-17-5
CMF C2 H6 O



IT **131118-73-5P**, Famciclovir monohydrate
(dehydration; prepn. of cryst. solid famciclovir forms I, II, III by crystn. from org. solvents and/or water)

IT **666832-88-8P**, Famciclovir methanol solvate
666832-89-9P, Famciclovir ethanol solvate
(prepn. of cryst. solid famciclovir forms I, II, III by crystn. from org. solvents and/or water)

L34 ANSWER 7 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
2003:66403 Document No. 138:394835 Synthesis and stereochemical characterisation of platinum(II) complexes with the antiviral agents penciclovir and famciclovir. Cerasino, Leonardo; Intini, Francesco P.; Kobe, Joze; de Clercq, Erik; Natile, Giovanni (Dipartimento Farmaco-Chimico, Universita degli Studi di Bari, Bari, I-70125, Italy). Inorganica Chimica Acta, 344, 174-182 (English) **2003.** CODEN: ICHAA3. ISSN: 0020-1693. OTHER SOURCES: CASREACT 138:394835. Publisher: Elsevier Science B.V..

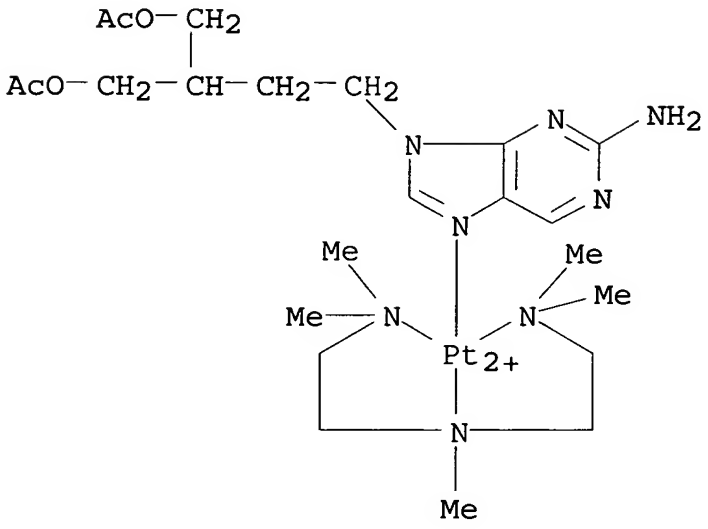
AB The synthesis and the stereochem. characterization of Pt complexes contg. one mol. of antiviral drug, penciclovir or famciclovir (L), and different sets of ancillary ligands (Clx(NH3)3-x, x = 1 or 2, and N,N,N',N'',N''-pentamethyldiethylenetriamine, pmdien) are reported. Penciclovir is a guanosine analog, while famciclovir is a prodrug of penciclovir lacking the O in position 6 of the purine ring. The study has allowed comparison of structural features of Pt derivs. with different bulk of the carrier ligand(s) and of the purines. NMR expts. (particularly diagnostic are the H8 and H6 chem. shifts of the purine) indicate that in compds. with non bulky carrier ligands (Clx(NH3)3-x) the purine is free to rotate about the Pt-N7 bond. In contrast, in complexes with bulky carrier ligand (pmdien) there is restricted rotation about the Pt-N7 bond and the purine is constrained in a quasi orthogonal position with respect to the Pt coordination plane. Because of the slow rotation for [Pt(pmdien)(L)]2+ two rotamers are obsd. in soln. differing for the relative positions of the six-membered ring of the purine and the central N-Me of pmdien with respect to the Pt coordination plane (on the same side or on opposite sides for endo and exo rotamers, resp.). Penciclovir, having an O atom in position 6 of the purine ring, favors the exo over the endo rotamer while famciclovir, having just a H atom in position 6, favors the endo over the exo rotamer. The change in rotamer preference suggests that intramol. interactions involving mostly the substituent in position 6 of the purine and the terminal N-methyls of pmdien have opposite character for the two antiviral ligands. Biol. tests confirmed that cationic Pt species cis-[PtCl(NH3)2(L)]+ can have cytotoxicity towards tumor cells greater than corresponding compds. cis-[PtCl2(NH3)(L)].

IT **526191-45-7P**
(prepn. and NMR spectra)
RN 526191-45-7 ZCAPLUS
CN Platinum(2+), [2-[2-(2-amino-9H-purin-9-yl-.kappa.N7)ethyl]-1,3-propanediyl diacetate][N-[2-(dimethylamino-.kappa.N)ethyl]-N,N',N'-trimethyl-1,2-ethanediamine-.kappa.N,.kappa.N']-, (SP-4-2)-,

dinitrate (9CI) (CA INDEX NAME)

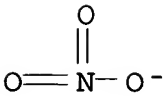
CM 1

CRN 526191-44-6
CMF C23 H42 N8 O4 Pt
CCI CCS



CM 2

CRN 14797-55-8
CMF N O3

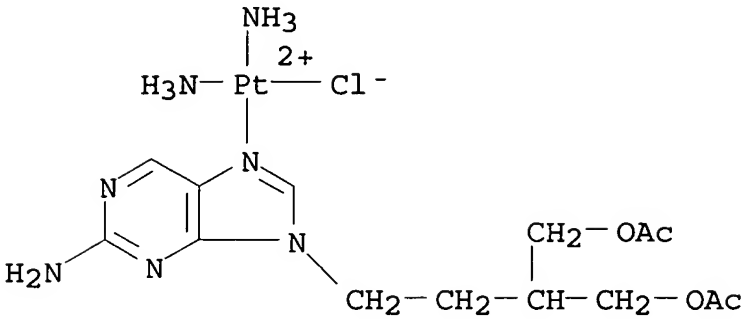


IT **526191-41-3P**
(prepn. of platinum(II) ammine penciclovir ammine complex)
RN 526191-41-3 ZCAPLUS
CN Platinum(1+), [2-[2-(2-amino-9H-purin-9-yl-.kappa.N7)ethyl]-1,3-propanediyl diacetate]diamminechloro-, (SP-4-3)-, nitrate (9CI) (CA INDEX NAME)

CM 1

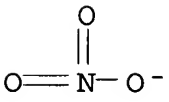
CRN 526191-40-2

CMF C14 H25 Cl N7 O4 Pt
CCI CCS



CM 2

CRN 14797-55-8
CMF N O3



IT **526191-45-7P**
(prepn. and NMR spectra)
IT **526191-41-3P**
(prepn. of platinum(II) ammine penciclovir ammine complex)

L34 ANSWER 8 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
2001:564833 Document No. 135:152367 Nitrate salts of antimicrobial agents. Del Soldato, Piero; Benedini, Francesca; Antognazza, Patrizia (Nicox S.A., Fr.). PCT Int. Appl. WO 2001054691 A1 **20010802**, 105 pp. DESIGNATED STATES: W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-EP430 20010116. PRIORITY: IT 2000-MI92 20000126.
AB Nitrate salts of antiviral, antifungal, and antibacterial agents such as acyclovir, tetracycline, etc. were prepd. Growth inhibition of, e.g., an S. Aureus strain by title compds. was demonstrated.
IT **352466-93-4P**

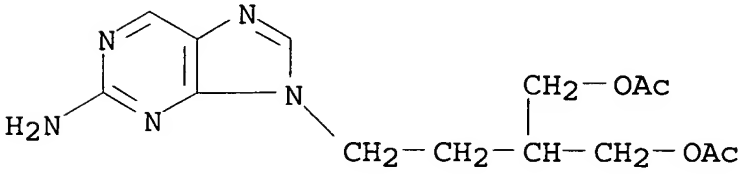
(nitrate salts of antimicrobial agents)

RN 352466-93-4 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, diacetate (ester), nitrate (salt) (9CI) (CA INDEX NAME)

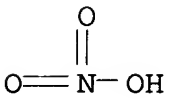
CM 1

CRN 104227-87-4
CMF C14 H19 N5 O4



CM 2

CRN 7697-37-2
CMF H N O3



IT **352466-93-4P**
(nitrate salts of antimicrobial agents)

L34 ANSWER 9 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

2001:454439 Document No. 135:313106 Pharmacokinetic studies of 2-amino-9-(3-acetoxymethyl-4-isopropoxycarbonyl-oxybut-1-yl)purine, an oral prodrug for the antiviral agent penciclovir. Choi, Won-Son; Im, Guang-Jin; Kim, Dae-Kee; Kim, Tae-Kon; Jung, Inho; Kim, Taek-Soo; Lee, Sung-Jae; Lee, Namkyu; Kim, Young-Woo; Kim, Jae-Sun; Chang, Kieyoung (S. Korea). Drug Metabolism and Disposition, 29(7), 945-949 (English) **2001.** CODEN: DMDSAI. ISSN: 0090-9556. Publisher: American Society for Pharmacology and Experimental Therapeutics.

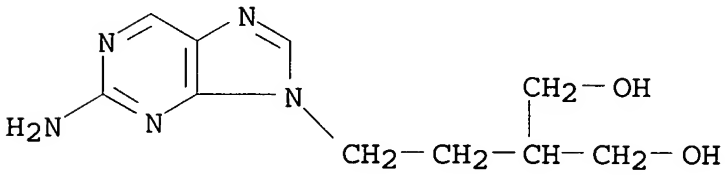
AB 2-Amino-9-(3-acetoxymethyl-4-isopropoxycarbonyloxybut-1-yl)purine (SK1899) was tested as an oral prodrug for penciclovir. SK1899 was administered orally to rats and dogs at doses up to 2 and 0.68 mmol/kg, resp. SK1899 was well absorbed, and the major metabolites detected in plasma and urine were penciclovir, the active antiviral

compd., and 6-deoxypenciclovir (M4) in both species. In rats, SK1899 was rapidly and extensively metabolized to penciclovir, which reached the peak plasma concn. (Cmax) of 39.5 .mu.M at 0.5 h after 0.2-mmol/kg dosing. The area under the plasma concn.-time curve (AUC) for penciclovir was 57.5 .mu.M.cntdot.h. After an oral dose of 0.034 mmol/kg to dogs, extensive conversion of SK1899 to penciclovir also occurred with slower rate of formation of penciclovir from M4 than in rats. The mean Cmax and AUC for penciclovir were 4.5 .mu.M at 2.7 h and 28.2 .mu.M.cntdot.h, resp. The 0- to 24-h urinary recovery of penciclovir represented 36.1 and 36.3% of dose to rats and dogs, resp. Radioactivity was found in fetuses following an oral administration of [14C]SK1899 to pregnant rats, but no significant accumulation was obsd. Although substantial milk transfer of [14C]SK1899 occurred in rats, the radioactivity in milk was rapidly cleared. The values of Cmax, AUC, and urinary recovery of penciclovir after dosing with SK1899 to rats and dogs were similar or slightly higher than those from famciclovir. These data indicate that introduction of an isopropoxy carbonate group into one of the two hydroxyl groups of M4 did not significantly alter the oral bioavailability of penciclovir compared with famciclovir.

IT **104227-86-3**
(pharmacokinetics of 2-amino-9-(3-acetoxymethyl-4-isopropoxycarbonyl-oxybut-1-yl)purine)

RN 104227-86-3 ZCAPLUS

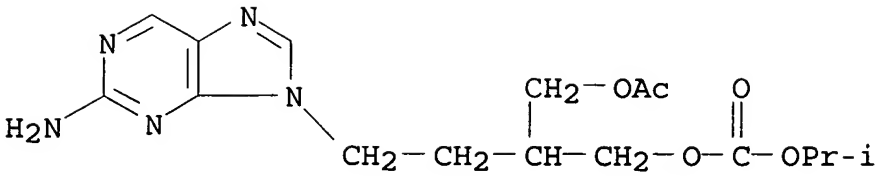
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



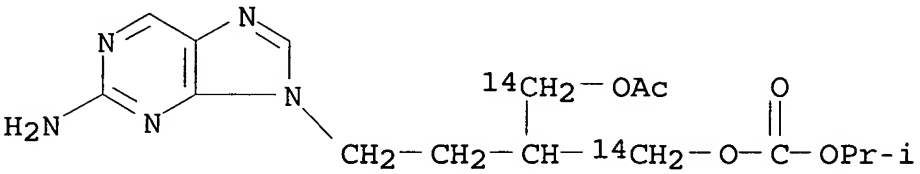
IT **247081-81-8**, SK 1899 **367968-18-1**
(pharmacokinetics of 2-amino-9-(3-acetoxymethyl-4-isopropoxycarbonyl-oxybut-1-yl)purine)

RN 247081-81-8 ZCAPLUS

CN Carbonic acid, 2-[(acetyloxy)methyl]-4-(2-amino-9H-purin-9-yl)butyl 1-methylethyl ester (9CI) (CA INDEX NAME)

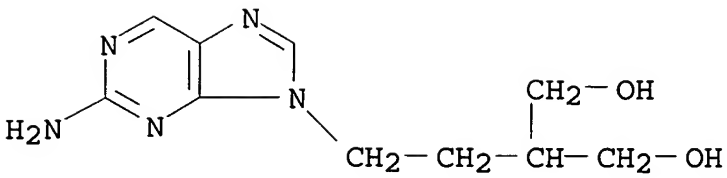


RN 367968-18-1 ZCAPLUS
CN Carbonic acid, 2-[(acetyloxy)methyl-14C]-4-(2-amino-9H-purin-9-yl)butyl-1-14C 1-methylethyl ester (9CI) (CA INDEX NAME)



IT **104227-86-3**
(pharmacokinetics of 2-amino-9-(3-acetoxymethyl-4-isopropoxycarbonyl-oxybut-1-yl)purine)
IT **247081-81-8**, SK 1899 **367968-18-1**
(pharmacokinetics of 2-amino-9-(3-acetoxymethyl-4-isopropoxycarbonyl-oxybut-1-yl)purine)

L34 ANSWER 10 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
2000:458477 Document No. 133:222945 A new route to famciclovir via palladium catalyzed allylation. Freer, Richard; Geen, Graham R.; Ramsay, Thomas W.; Share, Andrew C.; Slater, Graham R.; Smith, Neil M. (SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Essex, CM19 5AW, UK). Tetrahedron, 56(26), 4589-4595 (English) **2000.** CODEN: TETRAB. ISSN: 0040-4020. OTHER SOURCES: CASREACT 133:222945. Publisher: Elsevier Science Ltd..
AB An efficient route to the acyclic nucleoside analog famciclovir has been developed based on a palladium(0) catalyzed coupling of 2-amino-6-chloropurine and an allylic carbonate side-chain derived from 2,2-dimethyl-1,3-dioxan-5-one. The reaction proceeds via a highly N-9 regioselective purine allylation step involving a novel palladium mediated N-7 to N-9 rearrangement.
IT **246021-75-0P**
(prepn. of famciclovir via palladium catalyzed allylation)
RN 246021-75-0 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

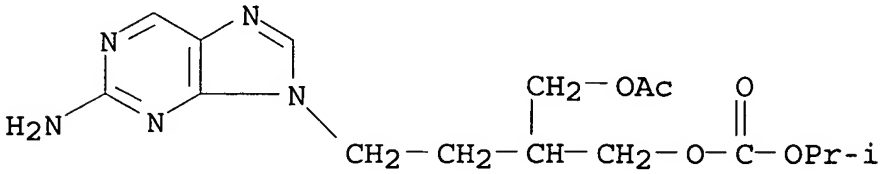
IT **246021-75-0P**
(prepn. of famciclovir via palladium catalyzed allylation)

L34 ANSWER 11 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
2000:310611 Document No. 133:68375 General pharmacology of the new antiviral agent SK 1899. Ryu, Keun Ho; Rhee, Hae In; Jung, Inho; Kim, Taek-Soo; Lee, Sung Jae; Im, Guang-Jin; Lee, Namkyu; Ryu, Do Hyun; Kim, Young-Woo; Kim, Jae-Jun; Chang, Kieyoung; Lee, Byung Ho; Shin, Hwa Sup; Kim, Eun-Joo; Kim, Key H.; Kim, Dae-Kee (Life Science Research Center, SK Chemicals, Suwon-Si, S. Korea). Arzneimittel-Forschung, 50(4), 395-403 (English) **2000.** CODEN: ARZNAD. ISSN: 0004-4172. Publisher: Editio Cantor Verlag.

AB The general pharmacol. properties of 2-amino-9-(3-acetoxymethyl-4-isopropoxycarbonyloxybut-1-yl)purine (CAS **247081-81-8**, SK 1899), a new potential antiviral agent, were investigated in mice, rats, guinea pigs, rabbits, and dogs. The oral administration of 50, 150, and 500 mg/kg of SK 1899 had no effects on the central nervous system except that it slightly increased the spontaneous locomotor activity in mice at a dose of 500 mg/kg. SK 1899 did not disturb either the spontaneous motility or contractor-induced contraction of the isolated organs such as guinea pig ileum, rat uterus, guinea pig vas deferens, and guinea pig trachea at concns. up to 10-4 mol/l. It slightly increased the contractile force in the isolated guinea pig atrium at a concn. of 10-4 mol/l. Following i.v. infusion of 5, 15, and 50 mg/kg of SK 1899 to anesthetized dogs, it did not change the mean arterial pressure, heart rate, left ventricular systolic pressure (LVSP), and respiratory rate, while it slightly increased the left ventricular pos. dP/dtmax (LV + dP/dtmax) at a dose of 50 mg/kg. SK 1899 did not induce any significant changes in the intestinal charcoal meal transit in mice, basal gastric juice secretion in rats, and renal function in rats. It did not affect the blood coagulation system and phenolsulfonphthalein secretion in rats. These findings suggest that SK 1899 has a very low potential to induce any adverse pharmacol. effects at the doses showing antiviral activity.

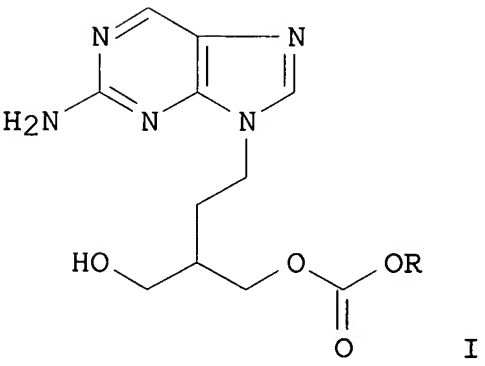
IT **247081-81-8**
(general pharmacol. of new antiviral agent SK 1899)

RN 247081-81-8 ZCAPLUS
CN Carbonic acid, 2-[(acetyloxy)methyl]-4-(2-amino-9H-purin-9-yl)butyl 1-methylethyl ester (9CI) (CA INDEX NAME)



IT **247081-81-8**
(general pharmacol. of new antiviral agent SK 1899)

L34 ANSWER 12 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
2000:179231 Document No. 132:189649 Antiviral drug preparations containing 2-amino-9-(3-hydroxymethyl-4-alkoxycarbonyloxy-1-butyl)purine derivatives. Kim, Dae-Kee; Lee, Nam-Kyu; Change, Kie-Young (Sunkyong Industry Ltd., S. Korea). Faming Zhuanli Shenqing Gongkai Shuomingshu CN 1192439 A **19980909**, 17 pp. (Chinese). CODEN: CNXXEV. APPLICATION: CN 1998-107140 19980305. PRIORITY: KR 1997-7148 19970305.
GI



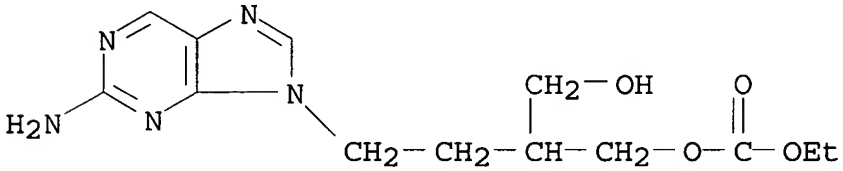
I

AB The title purine derivs. (I; R = alkyl) are prepd. by cyclizing 2-(2-benzyloxyethyl)propane-1,3-diol with 1,1'-carbonyldiimidazole in THF by refluxing for 3-72 h, reducing with H2 in THF and in the presence of 10% Pd/C catalyst at 10-50.degree. and H2 pressure of 15-60 psi, methylsulfonating in CH2Cl2 and in the presence of Et3N at (-20)-50.degree. for 1-24 h, substituting with

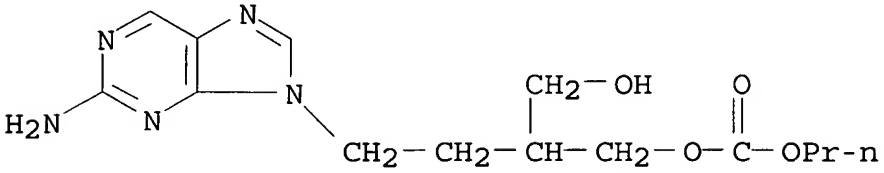
2-amino-6-chloropurine in DMF and in the presence of Cs2CO3 at 0-100.degree. for 1-72 h, reducing in CH3CN/DMF and in the presence of 10% Pd/C and Et3N at 10-50.degree. and H2 pressure of 15-60 psi, and ring-opening with alc.-CHCl3 in the presence of silica gel by refluxing. The medicinal compn. is composed of the purine deriv. or its medicinal salt, medicinal carrier or excipient, and/or additive. The medicinal compn. is used for prevention and treatment of infection induced by herpesvirus or hepatitis B virus.

IT **213273-25-7P 213273-26-8P 213273-27-9P 213273-28-0P 213273-30-4P 213273-31-5P 213273-32-6P**
(antiviral drug prepns. contg. 2-amino-9-(3-hydroxymethyl-4-alkoxycarbonyloxy-1-butyl)purine derivs.)

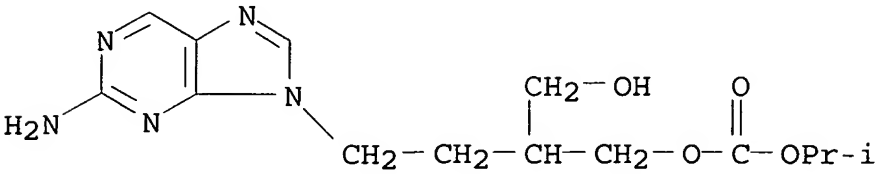
RN 213273-25-7 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl ethyl ester (9CI) (CA INDEX NAME)



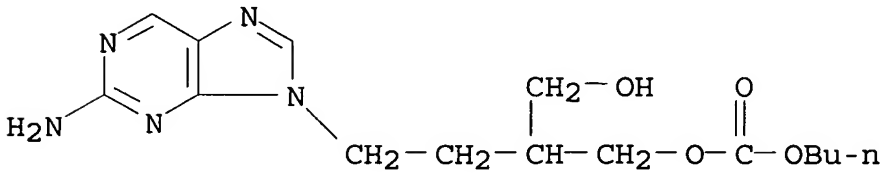
RN 213273-26-8 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl propyl ester (9CI) (CA INDEX NAME)



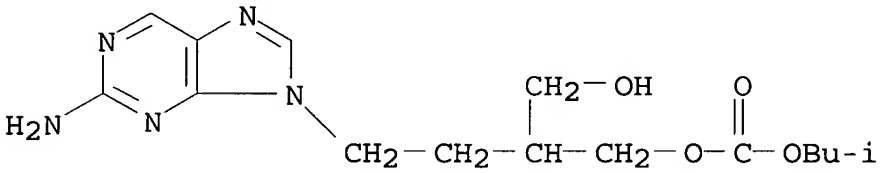
RN 213273-27-9 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl 1-methylethyl ester (9CI) (CA INDEX NAME)



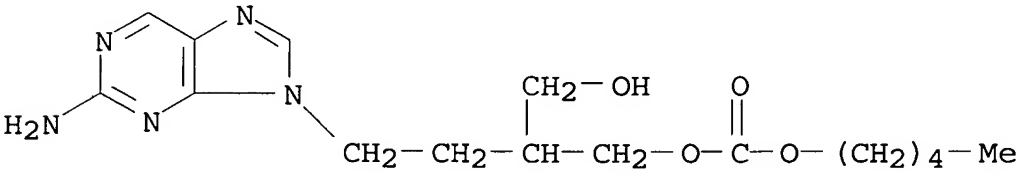
RN 213273-28-0 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl butyl ester (9CI) (CA INDEX NAME)



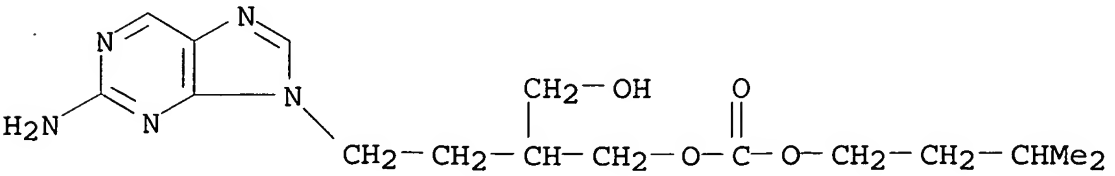
RN 213273-30-4 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl 2-methylpropyl ester (9CI) (CA INDEX NAME)



RN 213273-31-5 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl pentyl ester (9CI) (CA INDEX NAME)

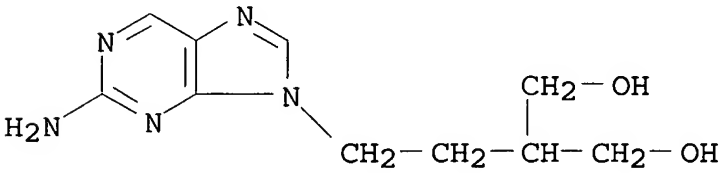


RN 213273-32-6 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl 3-methylbutyl ester (9CI) (CA INDEX NAME)



IT **213273-25-7P 213273-26-8P 213273-27-9P**
213273-28-0P 213273-30-4P 213273-31-5P
213273-32-6P
(antiviral drug prepns. contg. 2-amino-9-(3-hydroxymethyl-4-alkoxycarbonyloxy-1-butyl)purine derivs.)

L34 ANSWER 13 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
2000:171276 Document No. 132:207828 Synthesis of a new antiviral medicine famciclovir. Wang, En-si; Zhang, Guang-liang; Jin, Lei (College of Life Science, Jilin University, Changchun, 130023, Peop. Rep. China). Jilin Daxue Ziran Kexue Xuebao (1), 95-98 (Chinese) **2000.** CODEN: CLTTDI. ISSN: 0529-0279. Publisher: Jilin Daxue Ziran Kexue Xuebao Bianjibu.
AB The title compd. was prepd. with 21 % yield via regioselective alkylation of 2-aminopurine with 5-(2-bromoethyl)-2,2-dimethyl-1,3-dioxan as a pivotal step. The route without highly toxic reagents and high presure and temp. may be applied to industrial prodn.
IT **104227-86-3P**
(synthesis of a new antiviral medicine famciclovir)
RN 104227-86-3 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



IT **104227-86-3P**
(synthesis of a new antiviral medicine famciclovir)

L34 ANSWER 14 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
2000:98557 Document No. 132:137208 Preparation of antiviral alkyl substituted purine derivatives. Kobe, Joze; Jaksa, Suzana; Kalayanov, Genadij (Kemijski Institut, Slovenia). PCT Int. Appl. WO 2000006573 A1 **20000210**, 32 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-SI21 19990728. PRIORITY: SI

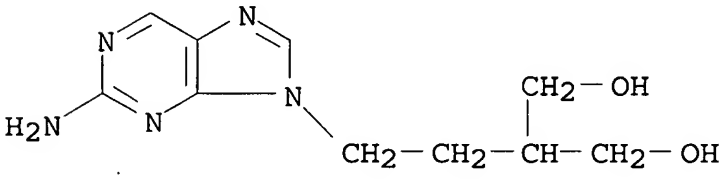
1998-216 19980729.

AB A new process for the prepn. of alkyl substituted purine derivs., esp. of N7 and N9 alkyl derivs. of purine, and to novel compds., namely N7 alkyl derivs. of purine endowed with a potential antiviral or antitumor activity, is described. This new process enables the regioselective coupling of a specific alkyl group in 7 or 9 position of purine. Thus, 4-acetoxy-3-acetoxymethylbutyl tosylate was added to N2-acetyl-7-benzylguanine (prepn. given), then reacted with Pd/C to give 9-(4-hydroxy-3-(hydroxymethyl)butyl)guanine in 47% yield.

IT **104227-86-3P**
(prepn. of alkyl substituted purine derivs. via regioselective coupling)

RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



IT **104227-86-3P**
(prepn. of alkyl substituted purine derivs. via regioselective coupling)

L34 ANSWER 15 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

1999:669272 Document No. 132:160838 Study on potential interactions of famciclovir with anticancer agents. Clarke, S. E.; Beedham, C.; Watanabe, Akihiro; Nomura, Hiromi; Yasuda, Eiichi (SmithKline Beecham Pharmaceuticals, Japan). Yakuri to Chiryo, 27(8), 1409-1415 (Japanese) **1999.** CODEN: YACHDS. ISSN: 0386-3603. Publisher: Raifu Saiensu Shuppan K.K..

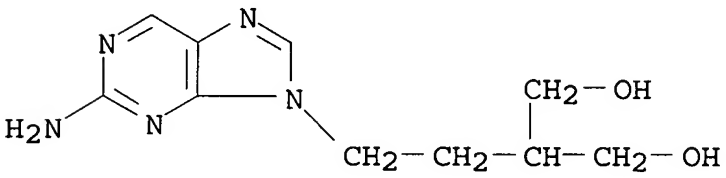
AB The potential for famciclovir, penciclovir, and 6-deoxypenciclovir to cause drug interactions with mercaptopurine, methotrexate, and 5-fluorouracil was investigated using fractions from rat, guinea pig, and human liver. Famciclovir, penciclovir, and 6-deoxypenciclovir did not inhibit mercaptopurine oxidization by xanthine oxidase at 100.mu. M. In contrast, the xanthine oxidase inhibitor, allopurinol, caused nearly complete inhibition. Famciclovir, penciclovir, and 6-deoxypenciclovir inhibited 7-hydroxylation of methotrexate by 23-35% at 100.mu. M, while the aldehyde oxidase inhibitors, menadione and isovanillin, at 100.mu. M, completely inhibited MTX hydroxylation. Famciclovir, penciclovir, and 6-deoxypenciclovir did not inhibit the metab. of 5-fluorouracil at 100.mu. M. In contrast, bromovinyluracil caused

marked inhibition. Based on these results, it is highly unlikely that famciclovir or penciclovir would cause clin. significant metab. based drug interactions with 6-mercaptopurine, methotrexate, or 5-fluorouracil.

IT **104227-86-3**, 6-Deoxypenciclovir
(study on potential interactions of famciclovir with anticancer agents)

RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)

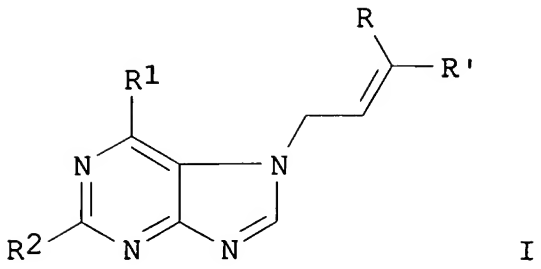


IT **104227-86-3**, 6-Deoxypenciclovir
(study on potential interactions of famciclovir with anticancer agents)

L34 ANSWER 16 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

1999:659387 Document No. 131:286768 Preparation of N-9-alkylated purine derivatives. Geen, Graham Richard; Share, Andrew Colin (Smithkline Beecham Plc, UK). PCT Int. Appl. WO 9951604 A2 **19991014**, 19 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-EP2309 19990330. PRIORITY: GB 1998-7116 19980402.

GI



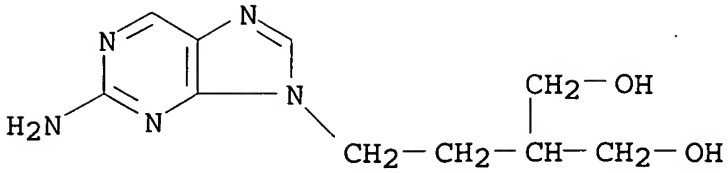
I

AB A method of rearranging N-7-alkylated purines [I; R, R' = H, C1-12 alkyl; R1, R2 = H, OH, halo, C1-12 alkyl, C2-12 alkenyl, (hetero)aryl, C1-12 alkyl- or aryl carbonate, amino, etc.] to form virucidal N-9-alkylated analogs by use of a Pd(0) catalyst in combination with a (diphenylphosphino)nC1-6 alkane (n = 1-6) is claimed. The invention also provides methods of making penciclovir and famciclovir using this rearrangement reaction. For example, stirring 2-amino-6-chloropurine and Me 2,2-dimethyl-5-ethenyl-1,3-dioxane-5-carbonate (prepn. from 2,2-dimethyl-1,3-dioxan-5-one, CH2:CHMgBr and ClCO2Me in 73% yield given) at 60.degree. in DMF in the presence of 1,2-bis(diphenylphosphino)ethane and tris(dibenzylidene) dipalladium(0).cntdot.CHCl3 compd. gave 61% 5-[2-(2-amino-6-chloropurin-9-yl)]ethylidene-2,2-dimethyl-1,3-dioxane which was hydrogenated for 18 h at 50.degree. in EtOAc in the presence of Pd/C and Et3N to give 74% 5-[2-(2-aminopurin-9-yl)ethyl]-2,2-dimethyl-1,3-dioxane. Acid hydrolysis of the latter with HCl in MeOH/THF gave 81% 2-amino-9-(4-hydroxy-3-hydroxymethylbut-1-yl)purine-HCl which was acetylated with Ac2O in CH2Cl2 the presence of 4-dimethylaminopyridine and Et3N to give 70% famciclovir.

IT **246021-75-0P**
(prepn. and acetylation; prepn. of N-9-alkylated purine derivs. as virucides)

RN 246021-75-0 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monohydrochloride (9CI) (CA INDEX NAME)

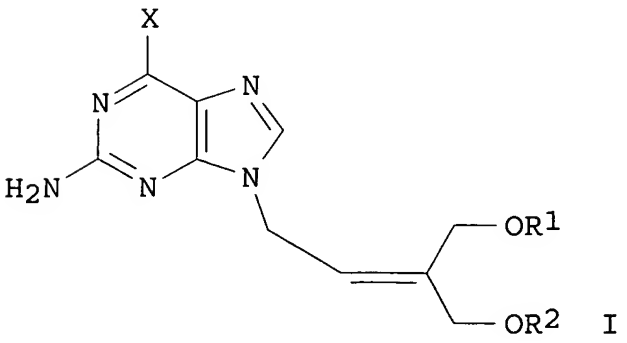


● HCl

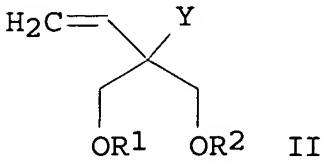
IT **246021-75-0P**
(prepn. and acetylation; prepn. of N-9-alkylated purine derivs. as virucides)

L34 ANSWER 17 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1999:659386 Document No. 131:286640 Process for the production of purine derivatives and intermediates. Freer, Richard; Geen, Graham Richard; Ramsay, Thomas Weir; Share, Andrew Colin; Smith, Neil Michael (Smithkline Beecham Plc, UK). PCT Int. Appl. WO 9951603 A1 **19991014**, 21 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-EP2308 19990330. PRIORITY: GB 1998-7114 19980402.

GI



I



II

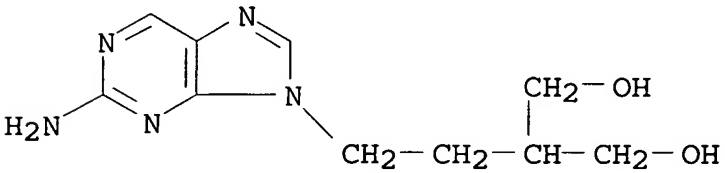
AB A process for the prodn. of a compd. of formula (I) (X = H, OH or

halo; R1, R2 independently = alkyl, aryl, alkylaryl, alkylsilyl, arylsilyl, alkylarylsilyl, or R1, R2 are joined together to form a cyclic acetal or ketal) is presented. The method comprises reacting a 2-amino-6-hydroxy or halopurine with a compd. of formula (II) (Y = a leaving group) in the presence of a palladium(0) catalyst and a ligand. The process provides a novel method for the prodn. of famciclovir and penciclovir.

IT **246021-75-0P**
(process for the prodn. of purine derivs. and intermediates)

RN 246021-75-0 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

IT **246021-75-0P**
(process for the prodn. of purine derivs. and intermediates)

L34 ANSWER 18 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

1999:571359 Document No. 131:295065 Synthesis and evaluation of 2-amino-9-(3-acyloxy methyl-4-alkoxycarbonyloxybut-1-yl)purines and 2-amino-9-(3-alkoxycarbonyloxymethyl-4-alkoxycarbonyloxybut-1-yl)purines as potential prodrugs of penciclovir. Kim, Dae-Kee; Lee, Namkyu; Ryu, Do Hyun; Kim, Young-Woo; Kim, Jae-Sun; Chang, Kieyoung; Im, Guang-Jin; Choi, Won-Son; Cho, Yong-Baik; Kim, Key H.; Colledge, Danni; Locarnini, Stephen (Life Science Research Center, SK Chemicals, Kvungki-Do, 440-745, S. Korea). Bioorganic & Medicinal Chemistry, 7(8), 1715-1725 (English) **1999.** CODEN: BMECEP. ISSN: 0968-0896. Publisher: Elsevier Science Ltd..

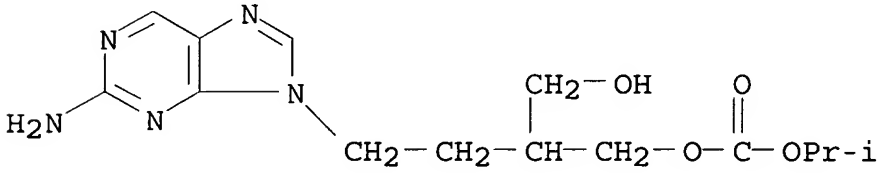
AB A series of 2-amino-9-(3-acyloxymethyl-4-alkoxycarbonyloxybut-1-yl)purines and 2-amino-9-(3-alkoxycarbonyloxymethyl-4-alkoxycarbonyloxybut-1-yl)purines were synthesized as potential prodrugs of penciclovir. Treatment of 6-deoxypenciclovir with tri-Me orthoacetate or tri-Et orthopropionate (1.2 equiv) in DMF in the presence of p-TsOH.cntdot.H2O (0.1 equiv) followed by quenching with excess H2O gave the corresponding mono-O-acetyl or mono-O-propionyl compd. in excellent yields of 95 and 92%, resp. Reactions of this mono-O-acetyl or mono-O-propionyl compd. with an

appropriate alkyl (Me, Et, n-Pr, and i-Pr) 4-nitrophenyl carbonate (1.2 equiv) in pyridine in the presence of a catalytic amt. of DMAP (0.1 equiv) at 80.degree.C afforded the monoacyl, monocarbonate derivs. of 6-deoxypenciclovir in 86-94% yields. Similar reactions of 6-deoxypenciclovir with 2.1 equiv of alkyl 4-nitrophenyl carbonate produced the dicarbonate derivs. in 81-83% yields. Of the prodrugs tested in rats, 2-amino-9-(3-acetoxymethyl-4-isopropoxycarbonyloxybut-1-yl)purine (I) achieved the highest mean urinary recovery of penciclovir (36%). The mean urinary recovery of penciclovir and concns. of penciclovir in the blood from I in mice were also slightly higher than those from famciclovir. The in vivo antiviral efficacy of I in HSV-1-infected normal BALB/c mice was higher than those of famciclovir and valaciclovir in terms of mortality (100, 80, and 40%) and mean survival time (> 21, 13.+-.5.0 (SEM), and 13.+-.1.6 days). Compd. I demonstrated an effective anti-hepadnaviral response with intrahepatic viral load being reduced by 90%, the viral supercoiled DNA levels reduced by 70% and Pre-S expression inhibited by 30% against duck hepatitis B virus (DHBV) in vivo, and did not cause any significant hepatotoxicity after 4 wk of treatment.

IT **213273-27-9**, SK 1875
(comparison with; synthesis and evaluation of purine derivs. as potential prodrugs of penciclovir)

RN 213273-27-9 ZCAPLUS

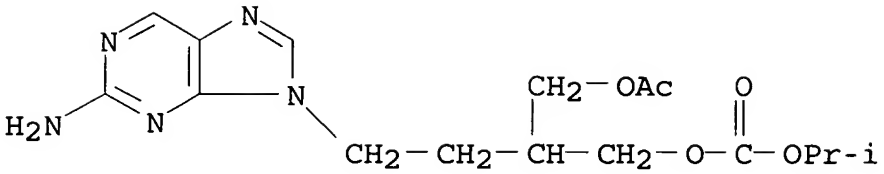
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl 1-methylethyl ester (9CI) (CA INDEX NAME)



IT **247081-81-8P**
(synthesis and evaluation of purine derivs. as potential prodrugs of penciclovir)

RN 247081-81-8 ZCAPLUS

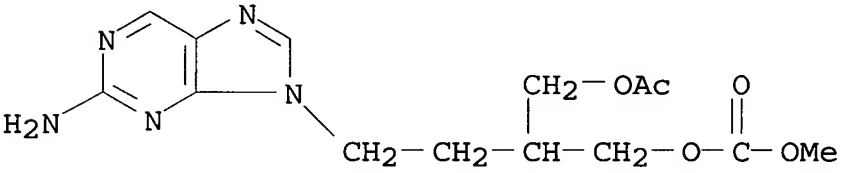
CN Carbonic acid, 2-[(acetyloxy)methyl]-4-(2-amino-9H-purin-9-yl)butyl 1-methylethyl ester (9CI) (CA INDEX NAME)



IT **247081-78-3P 247081-79-4P 247081-80-7P**
247081-82-9P 247081-83-0P 247081-84-1P
247081-85-2P 247081-86-3P 247081-87-4P
247081-88-5P 247081-89-6P
(synthesis and evaluation of purine derivs. as potential prodrugs of penciclovir)

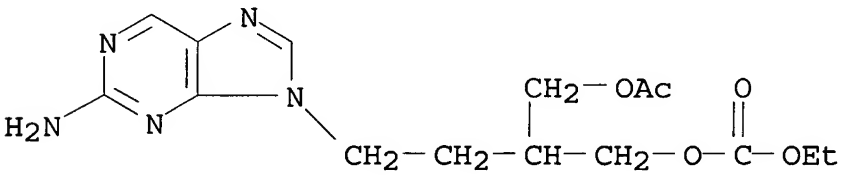
RN 247081-78-3 ZCAPLUS

CN Carbonic acid, 2-[(acetyloxy)methyl]-4-(2-amino-9H-purin-9-yl)butyl methyl ester (9CI) (CA INDEX NAME)



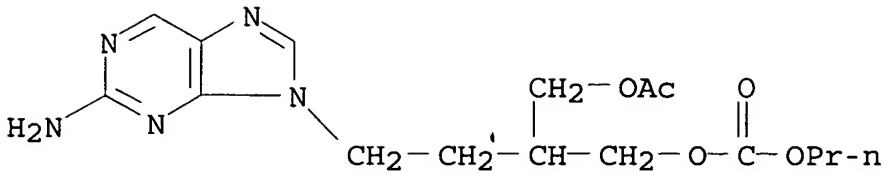
RN 247081-79-4 ZCAPLUS

CN Carbonic acid, 2-[(acetyloxy)methyl]-4-(2-amino-9H-purin-9-yl)butyl ethyl ester (9CI) (CA INDEX NAME)

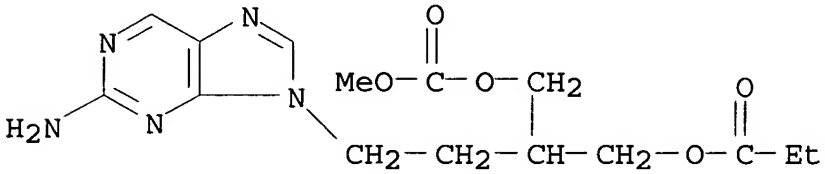


RN 247081-80-7 ZCAPLUS

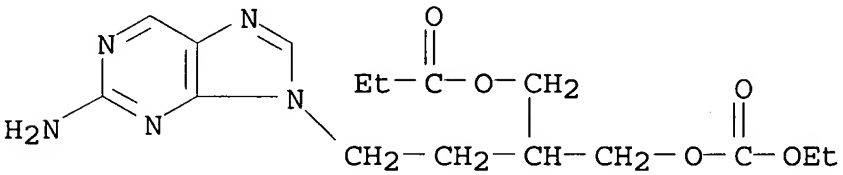
CN Carbonic acid, 2-[(acetyloxy)methyl]-4-(2-amino-9H-purin-9-yl)butyl propyl ester (9CI) (CA INDEX NAME)



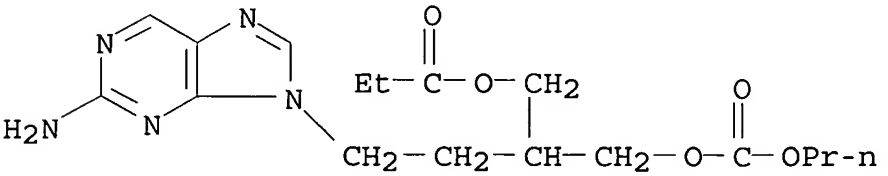
RN 247081-82-9 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-[(1-oxopropoxy)methyl]butyl methyl ester (9CI) (CA INDEX NAME)



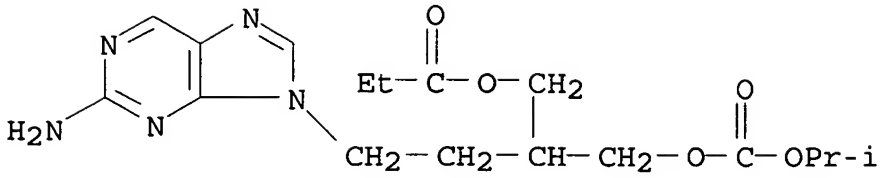
RN 247081-83-0 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-[(1-oxopropoxy)methyl]butyl ethyl ester (9CI) (CA INDEX NAME)



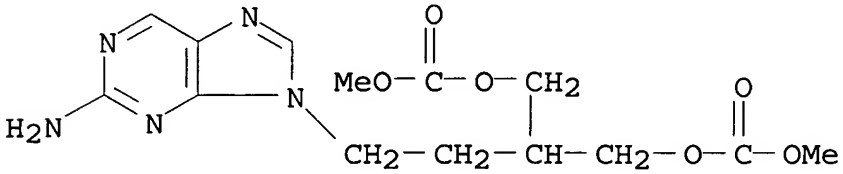
RN 247081-84-1 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-[(1-oxopropoxy)methyl]butyl propyl ester (9CI) (CA INDEX NAME)



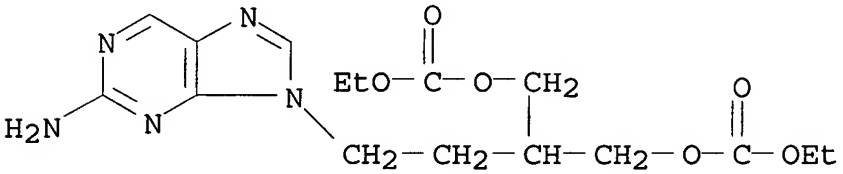
RN 247081-85-2 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-[(1-oxopropoxy)methyl]butyl 1-methylethyl ester (9CI) (CA INDEX NAME)



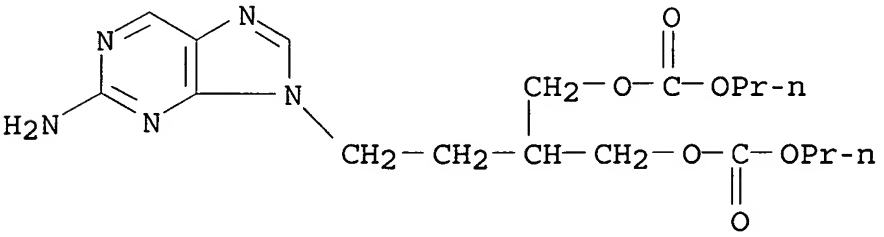
RN 247081-86-3 ZCAPLUS
CN Carbonic acid, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediyl dimethyl ester (9CI) (CA INDEX NAME)



RN 247081-87-4 ZCAPLUS
CN Carbonic acid, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediyl diethyl ester (9CI) (CA INDEX NAME)

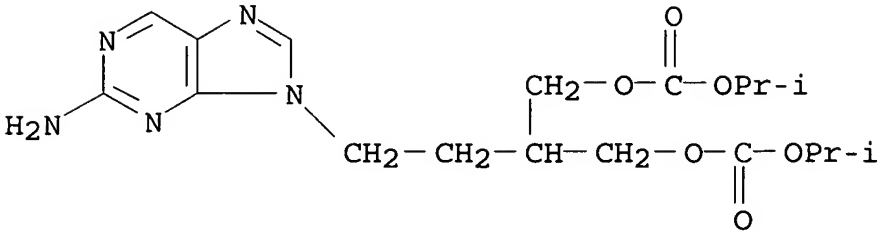


RN 247081-88-5 ZCAPLUS
CN Carbonic acid, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediyl dipropyl ester (9CI) (CA INDEX NAME)

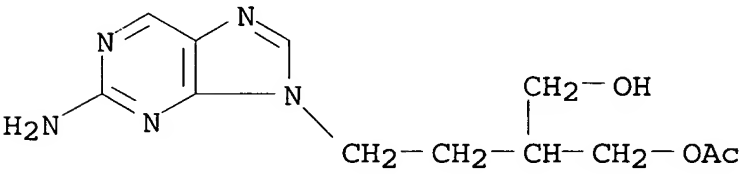


RN 247081-89-6 ZCAPLUS
CN Carbonic acid, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediyl

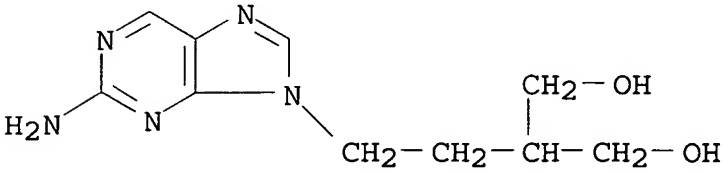
bis(1-methylethyl) ester (9CI) (CA INDEX NAME)



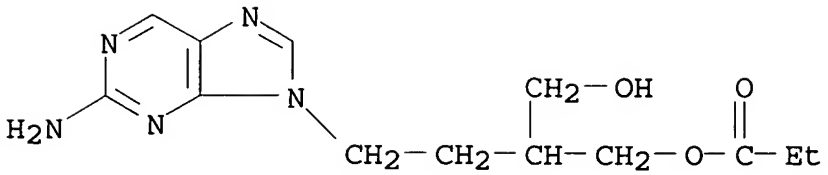
IT **104227-88-5P**
(synthesis and evaluation of purine derivs. as potential prodrugs of penciclovir)
RN 104227-88-5 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monoacetate (ester) (9CI) (CA INDEX NAME)



IT **104227-86-3**
(synthesis and evaluation of purine derivs. as potential prodrugs of penciclovir)
RN 104227-86-3 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



IT **125111-71-9P**
(synthesis and evaluation of purine derivs. as potential prodrugs of penciclovir)
RN 125111-71-9 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monopropanoate (ester) (9CI) (CA INDEX NAME)



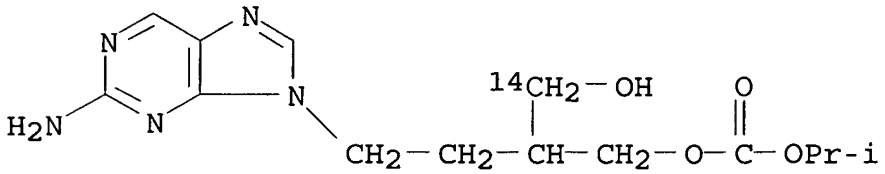
IT **213273-27-9**, SK 1875
(comparison with; synthesis and evaluation of purine derivs. as potential prodrugs of penciclovir)
IT **247081-81-8P**
(synthesis and evaluation of purine derivs. as potential prodrugs of penciclovir)
IT **247081-78-3P 247081-79-4P 247081-80-7P 247081-82-9P 247081-83-0P 247081-84-1P 247081-85-2P 247081-86-3P 247081-87-4P 247081-88-5P 247081-89-6P**
(synthesis and evaluation of purine derivs. as potential prodrugs of penciclovir)
IT **104227-88-5P**
(synthesis and evaluation of purine derivs. as potential prodrugs of penciclovir)
IT **104227-86-3**
(synthesis and evaluation of purine derivs. as potential prodrugs of penciclovir)
IT **125111-71-9P**
(synthesis and evaluation of purine derivs. as potential prodrugs of penciclovir)

L34 ANSWER 19 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1999:386145 Document No. 131:88120 Synthesis of carbon-14 labeled 2-amino-9-(3-hydroxymethyl-4-isopropoxycarbonyloxybut-1-yl)purine (SK 1875), a potential prodrug of penciclovir. Kim, Dae-Kee; Lee, Junwon; Kim, Youngseok; Lee, Namkyu; Kim, Young-Woo; Chang, Kieyoung; Kim, Jae-Sun; Lee, Kiseung; Kim, Key H. (Life Science Research Center, SK Chemicals, Kyungki-Do, 440-745, S. Korea). Journal of Labelled Compounds & Radiopharmaceuticals, 42(6), 597-604 (English) **1999.** CODEN: JLCRD4. ISSN: 0362-4803. Publisher: John Wiley & Sons Ltd..
AB The synthesis of 14C-2-amino-9-(3-hydroxymethyl-4-isopropoxycarbonyloxybut-1-yl)purine from [1-14C] di-Et malonate is described. The overall radiochem. yield of the product in a nine-step sequence was 16.1%, and the compd.'s radiochem. purity was 98.5%.
IT **229343-89-9P**
(prepn. of carbon-14 labeled 2-amino-9-(3-hydroxymethyl-4-

isopropoxycarbonyloxybut-1-yl)purine, a potential prodrug of penciclovir)

RN 229343-89-9 ZCAPLUS

CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl-14C)butyl 1-methylethyl ester (9CI) (CA INDEX NAME)



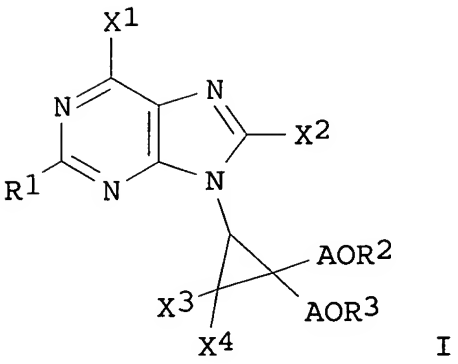
IT **229343-89-9P**

(prepn. of carbon-14 labeled 2-amino-9-(3-hydroxymethyl-4-isopropoxycarbonyloxybut-1-yl)purine, a potential prodrug of penciclovir)

L34 ANSWER 20 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

1999:380903 Document No. 131:5268 Preparation of purine derivatives having cyclopropane ring. Hayashi, Taketo; Yasuoka, Junichi; Nishiura, Akito (Sumika Fine Chemicals Co., Ltd., Japan). Eur. Pat. Appl. EP 916674 A1 **19990519**, 34 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1998-309170 19981110. PRIORITY: JP 1997-310839 19971112; JP 1998-133349 19980515; JP 1998-182765 19980629.

GI



I

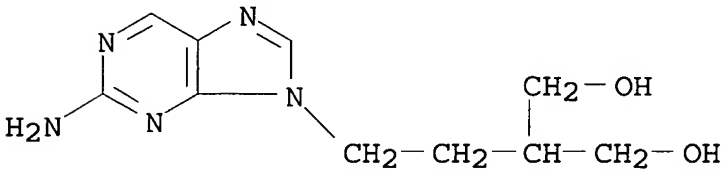
AB Cyclopropyl-substituted purine derivs. I (A = CH2, CO; X1 = H, halo,

alkoxy, OH; each of X2, X3, and X4 is independently H or halo; R1 = H, halo, protected or unprotected amino group; each of R2 and R3 is independently H or a substituted or unsubstituted alkyl group, a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted acyl group; in a case where A is CO, neither R2 nor R3 is a substituted or unsubstituted acyl group, and each of X3 and X4 is independently halo) were prepd. E.g., reaction of 2-amino-6-chloropurine with di-Me 2,2,2-trichloroethylidenemalonate gave 83.4% 2-amino-6-chloro-9-(3,3-dicarbomethoxy-2,2-dichlorocyclopropyl)purine. Treating the latter with H2/Pd under pressure gave 60.0% di-Me 2-(2-(2-aminopurin-9-yl)ethyl)malonate.

IT **104227-86-3P**
(prepn. and reactions of cyclopropyl-substituted purines)

RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



IT **104227-86-3P**
(prepn. and reactions of cyclopropyl-substituted purines)

L34 ANSWER 21 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

1999:347651 Document No. 131:124886 Aldehyde oxidase-catalyzed oxidation of methotrexate in the liver of guinea pig, rabbit and man. Jordan, C. Geraldine M.; Rashidi, Mohammed R.; Laljee, Hussain; Clarke, Stephen E.; Brown, John E.; Beedham, Christine (Department of Pharmaceutical Chemistry, School of Pharmacy, University of Bradford, Bradford, BD7 1DP, UK). Journal of Pharmacy and Pharmacology, 51(4), 411-418 (English) **1999.** CODEN: JPPMAB. ISSN: 0022-3573. Publisher: Royal Pharmaceutical Society of Great Britain.

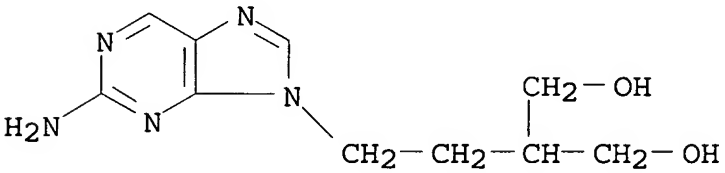
AB Although 7-hydroxymethotrexate is a major metabolite of methotrexate during high-dose therapy, negligible methotrexate-oxidizing activity has been found in-vitro in the liver in man. The goals of this study were to det. the role of aldehyde oxidase in the metab. of methotrexate to 7-hydroxymethotrexate in the liver and to study the effects of inhibitors and other substrates on the metab. of methotrexate. Methotrexate, (.+-.)-methotrexate and (-)-methotrexate were incubated with partially purified aldehyde oxidase from the liver of rabbit, guinea-pig and man and the products analyzed by HPLC. Rabbit liver aldehyde oxidase was used

for purposes of comparison. In-vitro aldehyde oxidase from the liver of man catalyzes the oxidn. of methotrexate to 7-hydroxymethotrexate, but the turnover is low. However, formation of 7-hydroxymethotrexate from all forms of methotrexate by the liver in guinea-pig and man was significantly inhibited in the presence of 100 .mu.M menadione and chlorpromazine, potent inhibitors of aldehyde oxidase. Allopurinol (100 .mu.M) had a negligible inhibitory effect on liver aldehyde oxidase from guinea-pig and man. Allopurinol is a xanthine oxidase inhibitor. The prodn. of 7-hydroxymethotrexate was enhanced in the presence of allopurinol. Although aldehyde oxidase is also responsible for some of this conversion, it is also possible that the closely related xanthine oxidase is responsible for the formation of 7-hydroxymethotrexate. By employing potent selective inhibitors of aldehyde oxidase, menadione and chlorpromazine, we have demonstrated for the first time that liver aldehyde oxidase from man is minimally involved in methotrexate oxidn.

IT **104227-86-3**
(effect of inhibitors on formation of 7-hydroxymethotrexate from methotrexate by liver aldehyde oxidase)

RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)

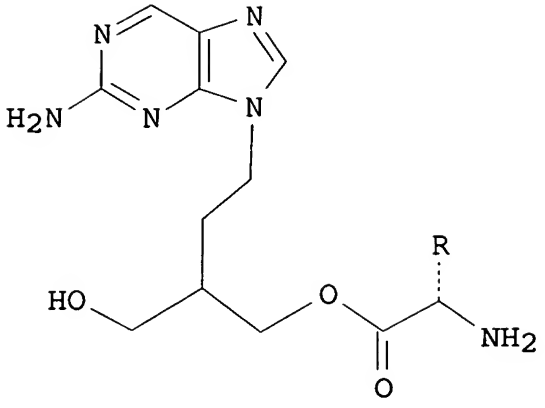


IT **104227-86-3**
(effect of inhibitors on formation of 7-hydroxymethotrexate from methotrexate by liver aldehyde oxidase)

L34 ANSWER 22 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

1999:224005 Document No. 130:338364 Synthesis and evaluation of amino acid esters of 6-deoxypenciclovir as potential prodrugs of penciclovir. Kim, Dae-Kee; Lee, Namkyu; Kim, Young-Woo; Chang, Kieyoung; Im, Guang-Jin; Choi, Won-Son; Kim, Key H. (Life Science Research Center, SK Chemicals, Kyungki-Do, 440-745, S. Korea). Bioorganic & Medicinal Chemistry, 7(2), 419-424 (English) **1999.** CODEN: BMECEP. ISSN: 0968-0896. Publisher: Elsevier Science Ltd..

GI



2 HCl

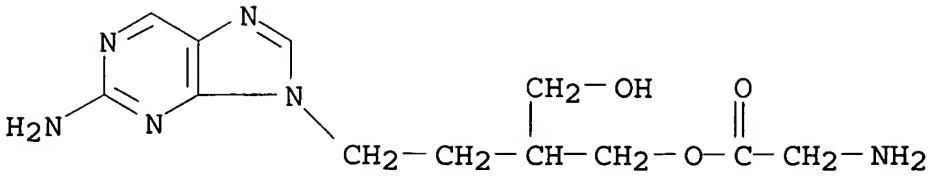
I

AB The amino acid ester derivs. (I; R = H, CH3, CH(CH3)2, CH2CH(CH3)2, CH(CH3)CH2CH3) of 6-deoxypenciclovir were synthesized as potential prodrugs of penciclovir, and were evaluated for their oral penciclovir bioavailability in mice and rats. Esterification of 6-deoxypenciclovir with N-carbo-benzyloxy-glycine, -L-alanine, -L-valine, -L-leucine, or -L-isoleucine (3.75 equiv.) using conventional coupling method (DCC/DMAP) afforded the mono-O-ester derivs. in 47-55% yields as a mixt. of two diastereomers along with the di-O-ester derivs. in 20-29% yields. Reductive cleavage of carbo-benzyloxy (Cbz) group (10% Pd/C, 1 atm. of H2, room temp. in methanol) followed by subsequent treatment of the resulting free amine with methanolic HCl soln. provided the mono-O-ester derivs. as di-HCl salt in 51-98% yields and the di-O-ester derivs. as tri-HCl salt in 65-98% yields. Of the prodrugs tested in mice and rats, 6-deoxypenciclovir O-L-valinate, O-L-isoleucinate, and O,O-di-glycinate showed significantly higher urinary recovery of penciclovir compared with that of penciclovir, but those are somewhat lower than that of famciclovir.

IT **224157-25-9P 224157-26-0P 224157-27-1P**
224157-28-2P 224157-29-3P 224157-30-6P
224157-31-7P 224157-32-8P 224157-33-9P
224157-34-0P
(prepn. and evaluation of amino acid esters of 6-deoxypenciclovir as potential prodrugs of penciclovir)

RN 224157-25-9 ZCAPLUS

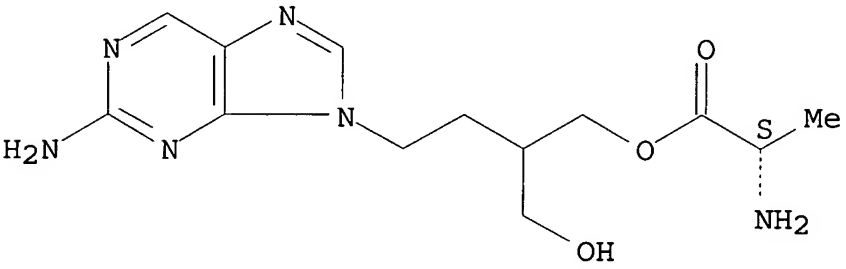
CN Glycine, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl ester, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

RN 224157-26-0 ZCAPLUS
CN L-Alanine, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl ester, dihydrochloride (9CI) (CA INDEX NAME)

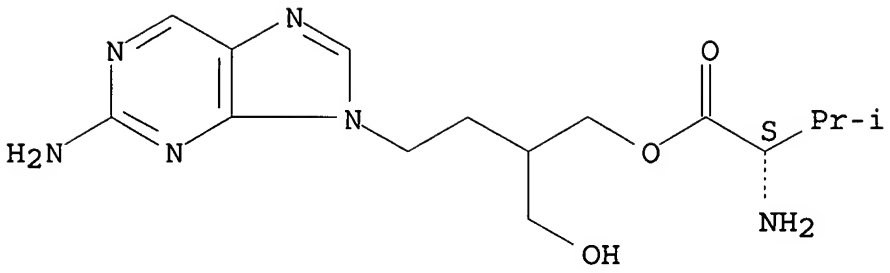
Absolute stereochemistry.



●2 HCl

RN 224157-27-1 ZCAPLUS
CN L-Valine, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl ester, dihydrochloride (9CI) (CA INDEX NAME)

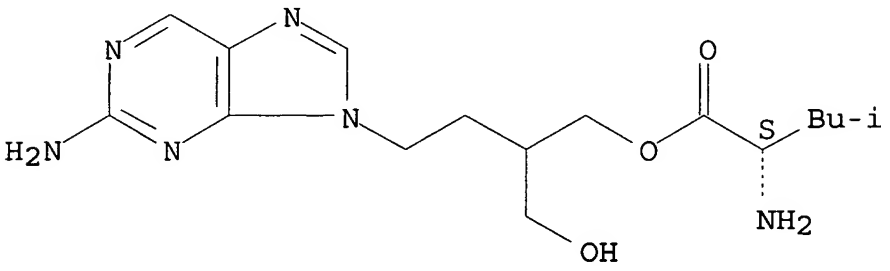
Absolute stereochemistry.



●2 HCl

RN 224157-28-2 ZCAPLUS
CN L-Leucine, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl ester, dihydrochloride (9CI) (CA INDEX NAME)

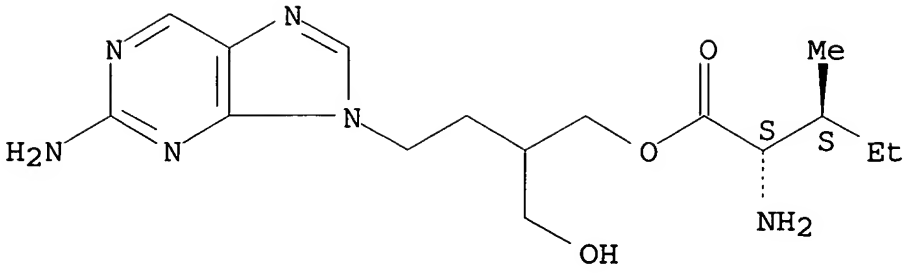
Absolute stereochemistry.



●2 HCl

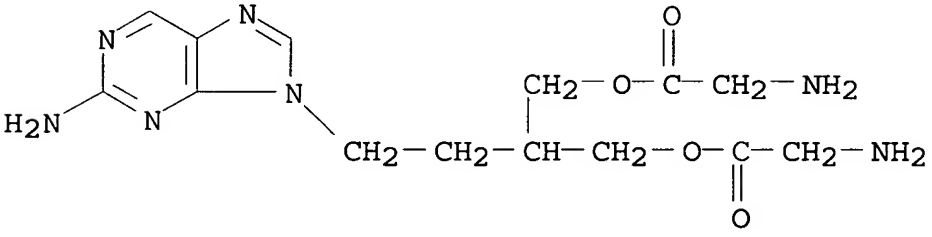
RN 224157-29-3 ZCAPLUS
CN L-Isoleucine, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 HCl

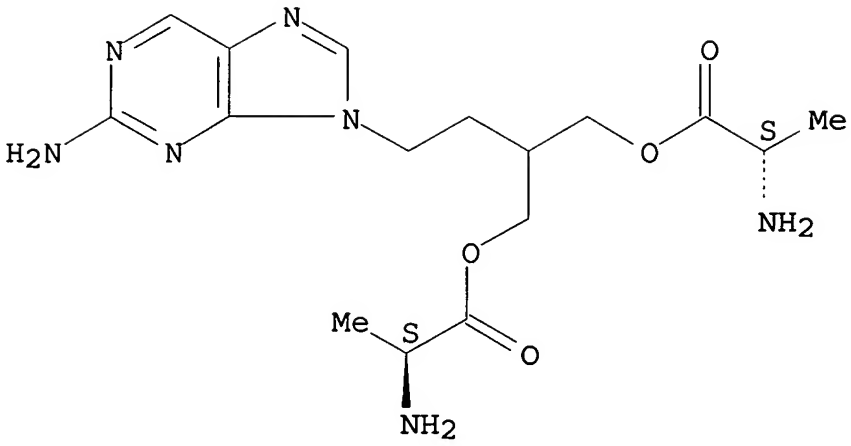
RN 224157-30-6 ZCAPLUS
CN Glycine, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediyl ester, trihydrochloride (9CI) (CA INDEX NAME)



●3 HCl

RN 224157-31-7 ZCAPLUS
CN L-Alanine, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediyl ester, trihydrochloride (9CI) (CA INDEX NAME)

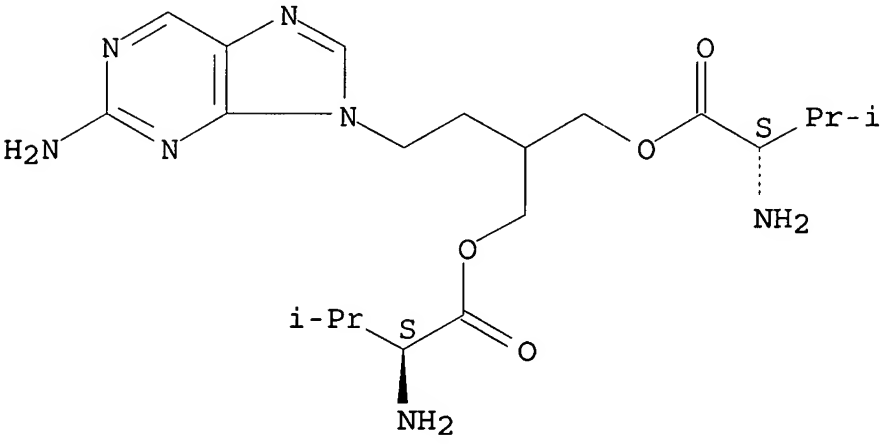
Absolute stereochemistry.



●3 HCl

RN 224157-32-8 ZCAPLUS
CN L-Valine, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediyl ester, trihydrochloride (9CI) (CA INDEX NAME)

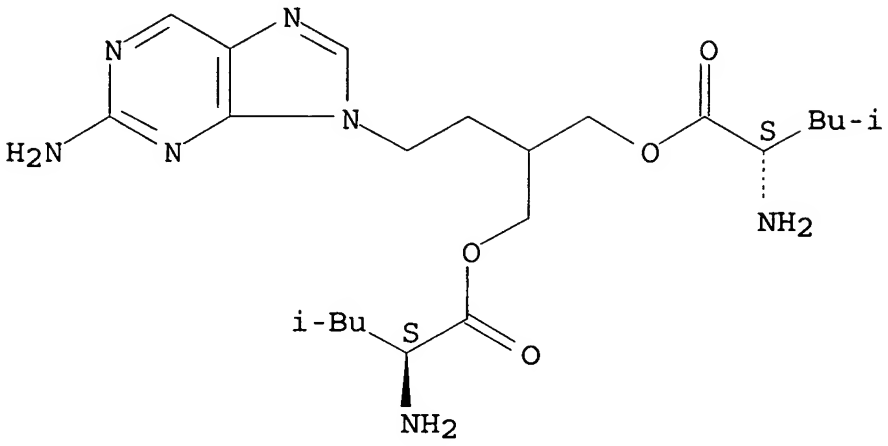
Absolute stereochemistry.



●3 HCl

RN 224157-33-9 ZCAPLUS
CN L-Leucine, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediyl ester, trihydrochloride (9CI) (CA INDEX NAME)

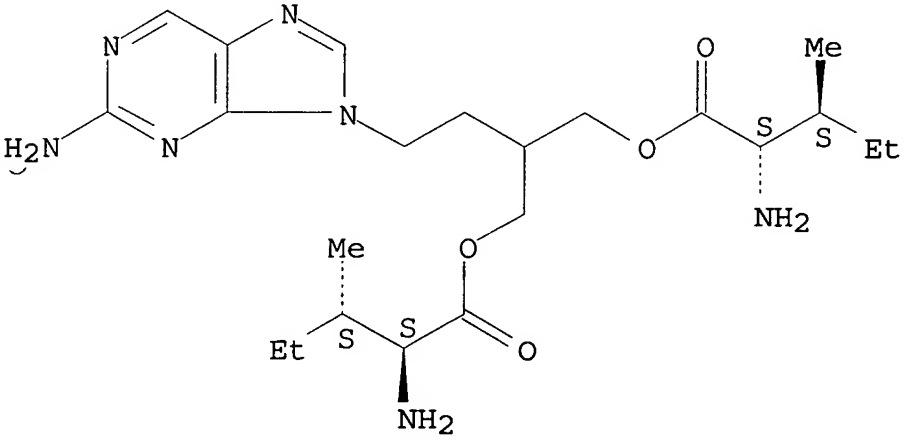
Absolute stereochemistry.



●3 HCl

RN 224157-34-0 ZCAPLUS
CN L-Isoleucine, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediyl ester, trihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

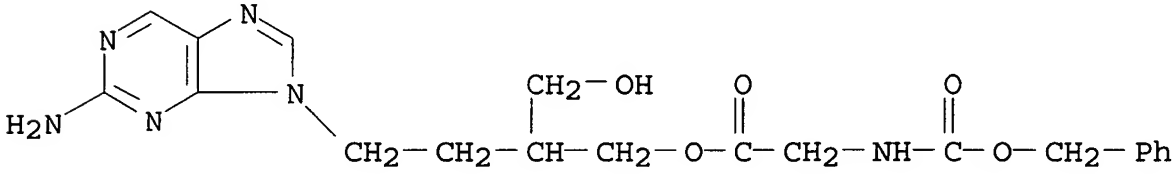


●3 HCl

IT **224157-15-7P 224157-16-8P 224157-17-9P**

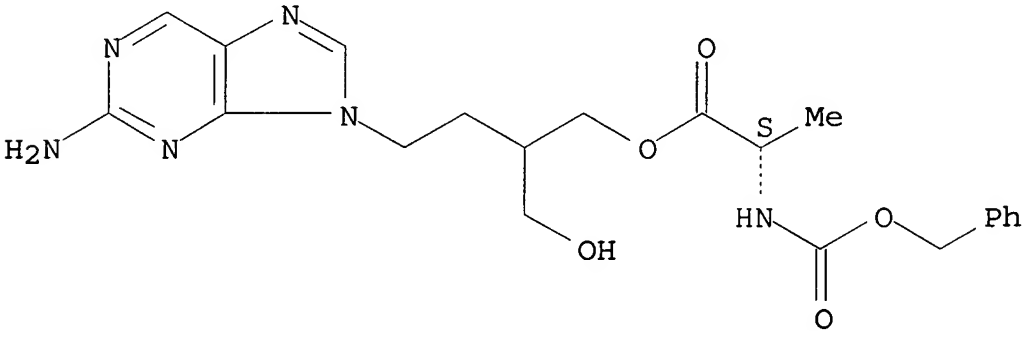
224157-18-0P 224157-19-1P 224157-20-4P
224157-21-5P 224157-22-6P 224157-23-7P
224157-24-8P
(prepn. and reaction of in the synthesis of amino acid esters of 6-deoxypenciclovir as potential prodrugs of penciclovir)

RN 224157-15-7 ZCAPLUS
CN Glycine, N-[(phenylmethoxy)carbonyl]-, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl ester (9CI) (CA INDEX NAME)



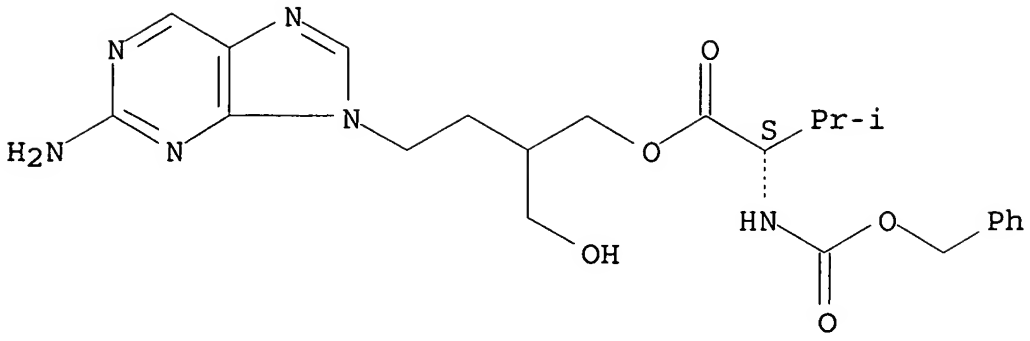
RN 224157-16-8 ZCAPLUS
CN L-Alanine, N-[(phenylmethoxy)carbonyl]-, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



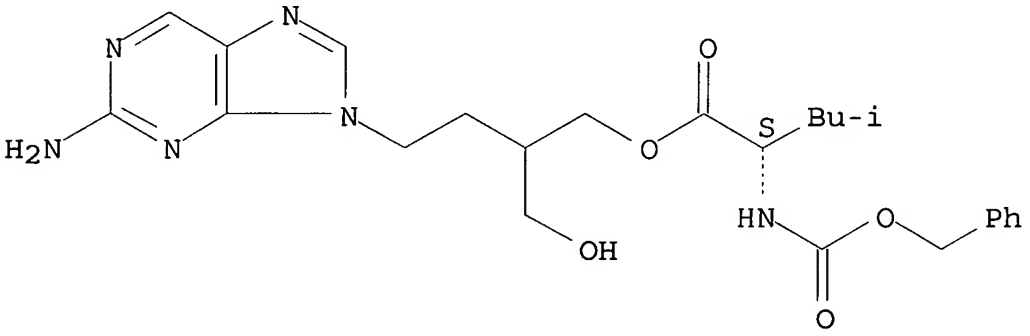
RN 224157-17-9 ZCAPLUS
CN L-Valine, N-[(phenylmethoxy)carbonyl]-, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



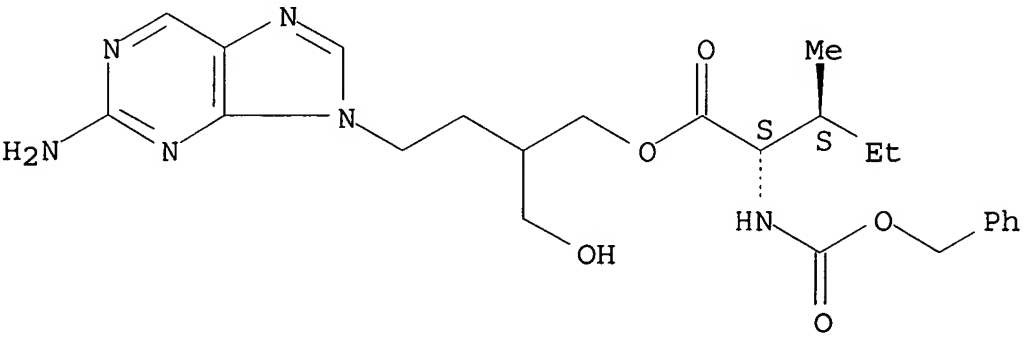
RN 224157-18-0 ZCAPLUS
CN L-Leucine, N-[(phenylmethoxy)carbonyl]-, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

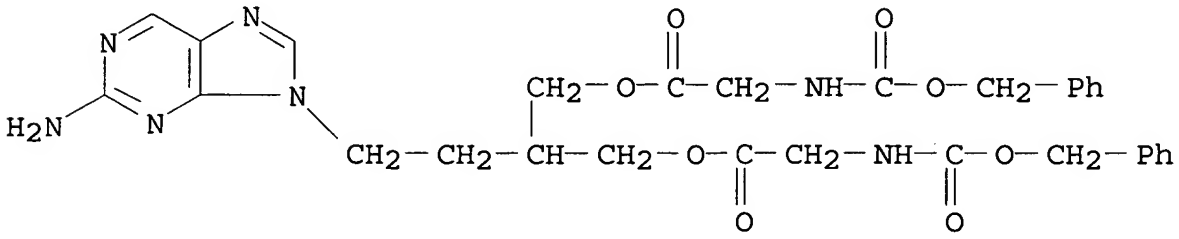


RN 224157-19-1 ZCAPLUS
CN L-Isoleucine, N-[(phenylmethoxy)carbonyl]-, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

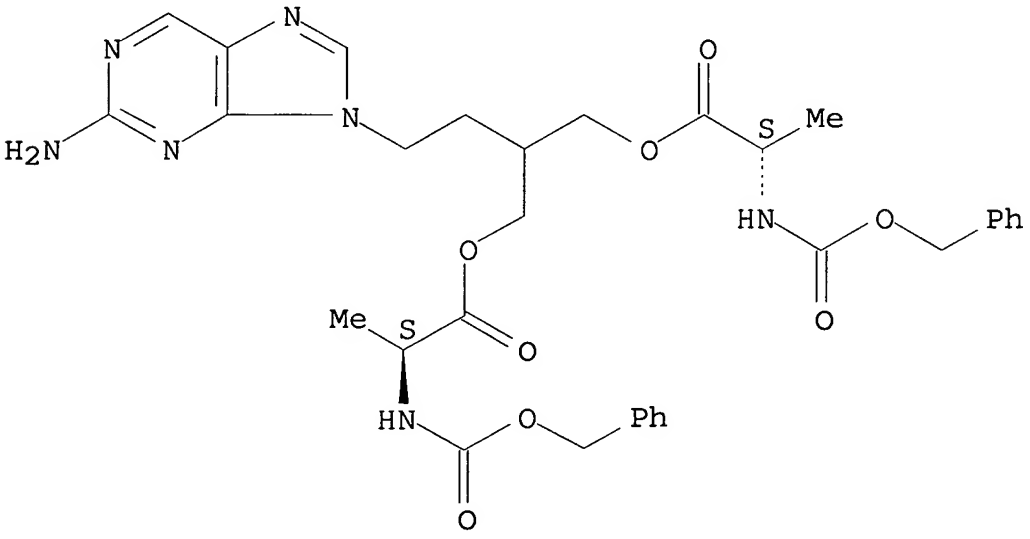


RN 224157-20-4 ZCAPLUS
CN Glycine, N-[(phenylmethoxy)carbonyl]-, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediyl ester (9CI) (CA INDEX NAME)



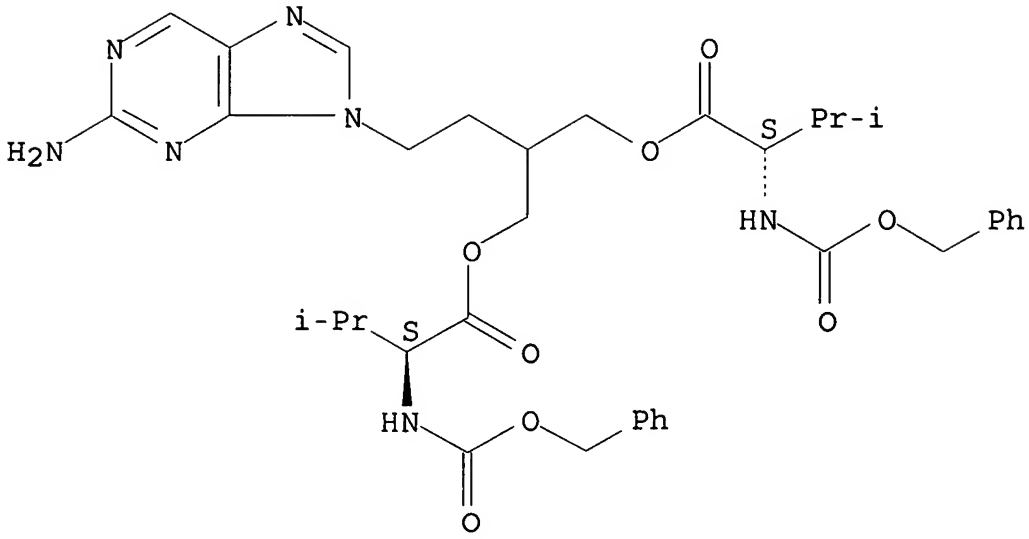
RN 224157-21-5 ZCAPLUS
CN L-Alanine, N-[(phenylmethoxy)carbonyl]-, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



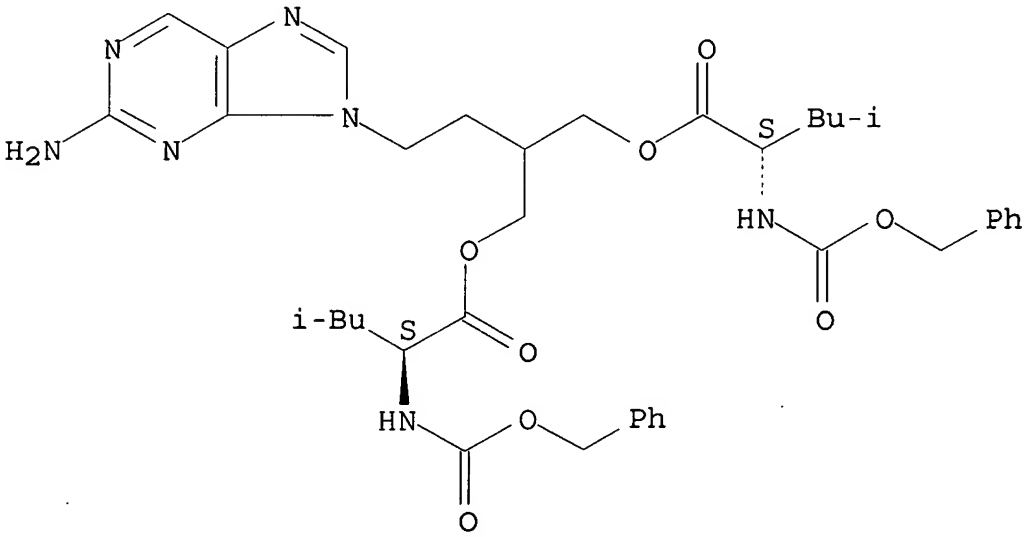
RN 224157-22-6 ZCAPLUS
CN L-Valine, N-[(phenylmethoxy)carbonyl]-, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



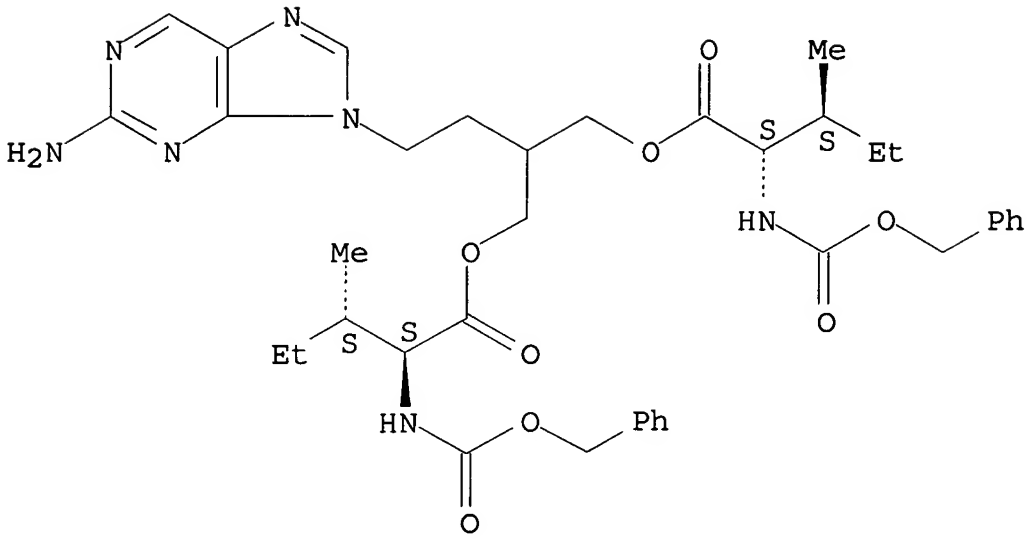
RN 224157-23-7 ZCAPLUS
CN L-Leucine, N-[(phenylmethoxy)carbonyl]-, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

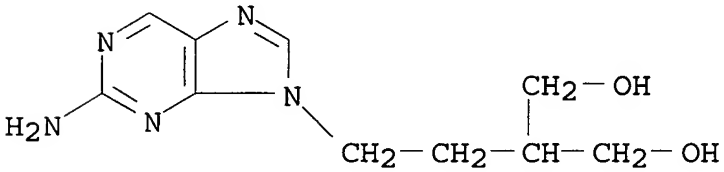


RN 224157-24-8 ZCAPLUS
CN L-Isoleucine, N-[(phenylmethoxy)carbonyl]-, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **104227-86-3**
(reaction of in the synthesis of amino acid esters of 6-deoxypenciclovir as potential prodrugs of penciclovir)
RN 104227-86-3 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)

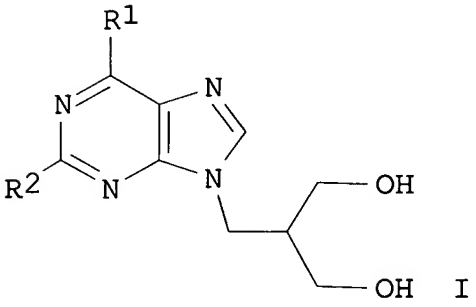


IT **224157-25-9P 224157-26-0P 224157-27-1P**
224157-28-2P 224157-29-3P 224157-30-6P
224157-31-7P 224157-32-8P 224157-33-9P
224157-34-0P
(prepn. and evaluation of amino acid esters of 6-deoxypenciclovir as potential prodrugs of penciclovir)
IT **224157-15-7P 224157-16-8P 224157-17-9P**
224157-18-0P 224157-19-1P 224157-20-4P
224157-21-5P 224157-22-6P 224157-23-7P
224157-24-8P
(prepn. and reaction of in the synthesis of amino acid esters of 6-deoxypenciclovir as potential prodrugs of penciclovir)
IT **104227-86-3**
(reaction of in the synthesis of amino acid esters of

6-deoxypenciclovir as potential prodrugs of penciclovir)

L34 ANSWER 23 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1999:194142 Document No. 130:209925 Preparation of purine acyclonucleosides as antiviral agents. Marcuccio, Sebastian Mario; Jarvis, Karen Elizabeth (Commonwealth Scientific and Industrial Research Organisation, Australia). PCT Int. Appl. WO 9912927 A1 **19990318**, 56 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-AU748 19980911. PRIORITY: AU 1997-9129 19970911.

GI



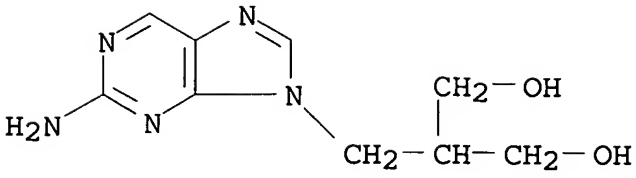
I

AB Purine acyclonucleosides I where: R1 is hydrogen, halogen, hydroxy, azido, alkoxy, aryloxy, thio, alkylthio, amino, alkylamino, hydrazino, hydroxylamino, benzyloxy, NRR' or NRCOR'; R2 is hydrogen, halogen, hydroxy, azido, alkoxy, aryloxy, thio, alkylthio, amino, alkylamino, hydrazino, hydroxylamino, benzyloxy, NRR' or NRCOR'; and R and R' are independently selected from hydrogen, alkyl and aryl; or a salt and pharmaceutically acceptable derivs. thereof; in the treatment and/or prophylaxis of hepatitis B viral infection. Thus, 9-[3-hydroxy-2-hydroxymethylprop-1-yl]guanine was prepd. and tested for its antiviral activity in human cells with hepatitis B (EC50 = 0.16 .mu.M).

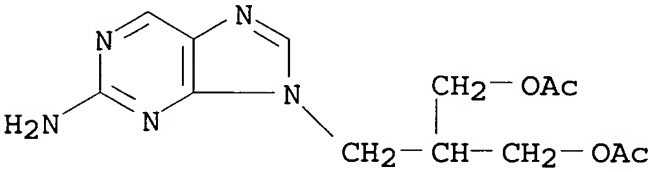
IT **220984-26-9P 220984-30-5P 220984-53-2P**
(prepn. of purine acyclonucleosides as antiviral agents)

RN 220984-26-9 ZCAPLUS

CN 1,3-Propanediol, 2-[(2-amino-9H-purin-9-yl)methyl]- (9CI) (CA INDEX NAME)

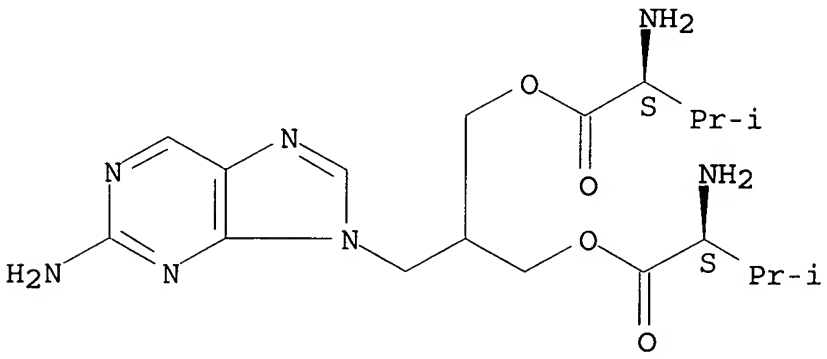


RN 220984-30-5 ZCAPLUS
CN 1,3-Propanediol, 2-[(2-amino-9H-purin-9-yl)methyl]-, diacetate (ester) (9CI) (CA INDEX NAME)



RN 220984-53-2 ZCAPLUS
CN L-Valine, 2-[(2-amino-9H-purin-9-yl)methyl]-1,3-propanediyl ester, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

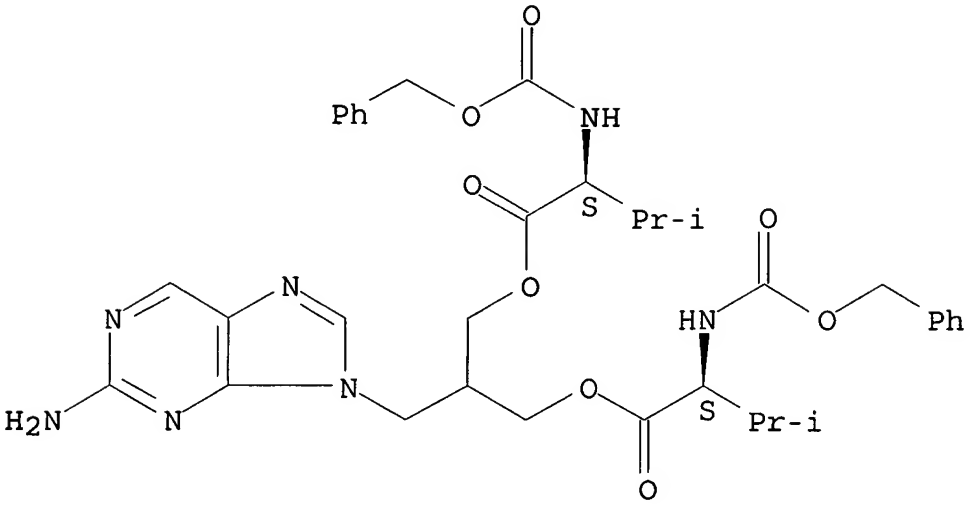


●2 HCl

IT **220984-51-0P**
(prepn. of purine acyclonucleosides as antiviral agents)
RN 220984-51-0 ZCAPLUS
CN 5,9-Dioxa-2,12-diazatridecanedioic acid, 7-[(2-amino-9H-purin-9-yl)methyl]-3,11-bis(1-methylethyl)-4,10-dioxo-, bis(phenylmethyl)

ester, (3S,11S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **220984-26-9P 220984-30-5P 220984-53-2P**
(prepn. of purine acyclonucleosides as antiviral agents)
IT **220984-51-0P**
(prepn. of purine acyclonucleosides as antiviral agents)

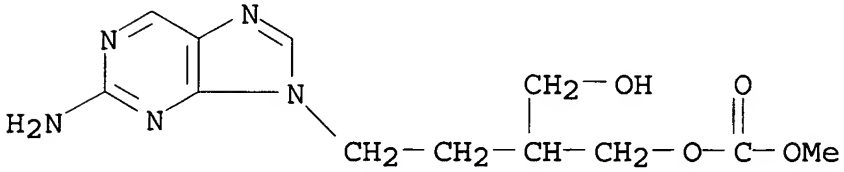
L34 ANSWER 24 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1998:499528 Document No. 129:239443 Synthesis and Evaluation of 2-Amino-9-(3-hydroxymethyl-4-alkoxycarbonyloxybut-1-yl)purines as Potential Prodrugs of Penciclovir. Kim, Dae-Kee; Lee, Namkyu; Kim, Young-Woo; Chang, Kieyoung; Kim, Jae-Sun; Im, Guang-Jin; Choi, Won-Son; Jung, Inho; Kim, Taek-Soo; Hwang, Yong-Youn; Min, Dong-Sun; Um, Key An; Cho, Yong-Baik; Kim, Key H. (Life Science Research Center, SK Chemicals, Changan-Ku Suwon-Si Kyungki-Do, 440-745, S. Korea). Journal of Medicinal Chemistry, 41(18), 3435-3441 (English) **1998.** CODEN: JMCMAR. ISSN: 0022-2623. Publisher: American Chemical Society.
AB A series of 2-amino-9-(3-hydroxymethyl-4-alkoxycarbonyloxybut-1-yl)purines and 2-amino-9-(2-(2-oxo-1,3-dioxan-5-yl)ethyl)purine (I) were synthesized as potential prodrugs of penciclovir and evaluated for their oral penciclovir bioavailability in mice and rats. Treatment of 2-(2-benzyloxyethyl)propane-1,3-diol with 1,1'-carbonyldiimidazole in THF followed by hydrogenolytic removal of the benzyl group of the resulting cyclic carbonate gave 5-(2-hydroxyethyl)-1,3-dioxan-2-one. Mesylation of the alc. obtained and then a coupling reaction of the resulting mesylate with 2-amino-6-chloropurine using anhyd. Cs2CO3 in DMF afforded 2-amino-6-chloro-9-(2-(2-oxo-1,3-dioxan-5-yl)ethyl)purine after

purifn. by flash column chromatog. on silica gel using EtOAc/MeCN/Et3N as eluent. Hydrogenation of the 6-chloro cyclic carbonate obtained followed by a ring-opening reaction of the 6-deoxy cyclic carbonate I in a mixt. of an appropriate alc. and CHCl3 using activated SiO2 as a Lewis acid afforded the corresponding alkyl monocarbonate derivs. in fair to good yields. Of the prodrugs tested in mice, the iso-Pr monocarbonate achieved the highest mean urinary recovery of penciclovir (53%), followed in order by the Pr monocarbonate (51%), the isopentyl monocarbonate (51%), the Et monocarbonate (50%), and famciclovir (48%). In rats, the alkyl monocarbonates showed levels of mean urinary recovery of penciclovir similar to that from famciclovir (39-41% vs. 40%, resp.). The alkyl monocarbonates were found to be quite stable in the aq. buffer solns., and among them, iso-Pr monocarbonate was the most stable with the half-lives (t1/2) of 88, >200, 61, and 26 days at pH 1.2, 6.0, 7.4, and 8.0, resp. In addn., iso-Pr monocarbonate was highly sol. in H2O (138.8 mg/mL, 20.degree.).

IT **104227-97-6P 213273-25-7P 213273-26-8P 213273-27-9P 213273-28-0P 213273-30-4P 213273-31-5P 213273-32-6P**
(synthesis and evaluation of 2-amino-9-(3-hydroxymethyl-4-alkoxycarbonyloxybut-1-yl)purines as potential prodrugs of penciclovir)

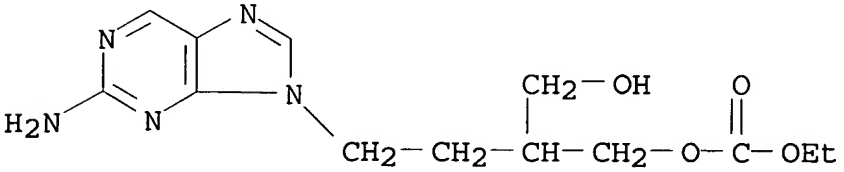
RN 104227-97-6 ZCAPLUS

CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl methyl ester (9CI) (CA INDEX NAME)



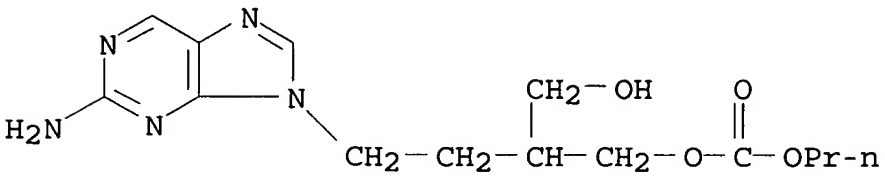
RN 213273-25-7 ZCAPLUS

CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl ethyl ester (9CI) (CA INDEX NAME)

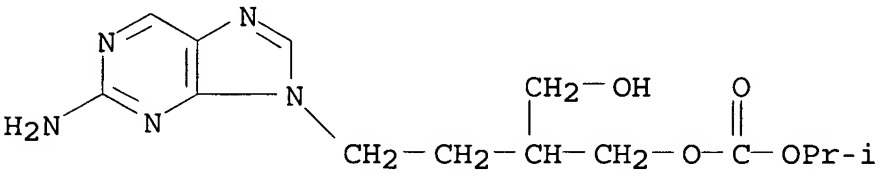


RN 213273-26-8 ZCAPLUS

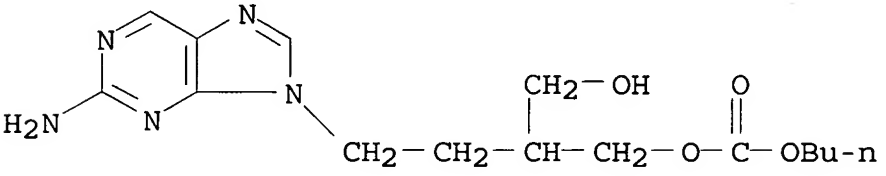
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl propyl ester (9CI) (CA INDEX NAME)



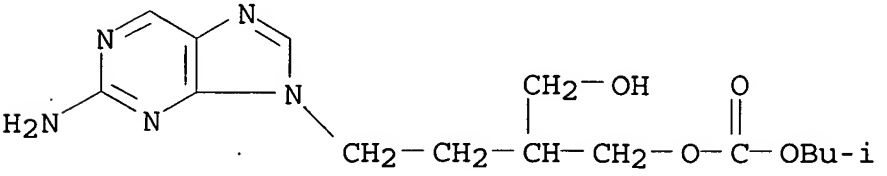
RN 213273-27-9 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl 1-methylethyl ester (9CI) (CA INDEX NAME)



RN 213273-28-0 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl butyl ester (9CI) (CA INDEX NAME)

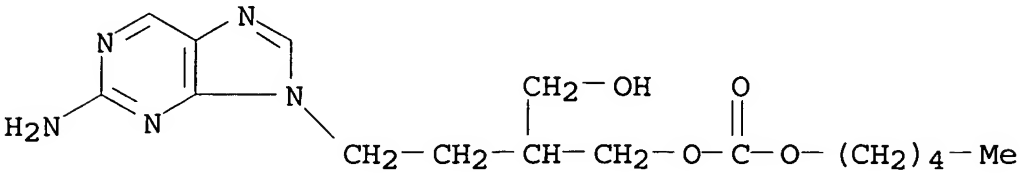


RN 213273-30-4 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl 2-methylpropyl ester (9CI) (CA INDEX NAME)

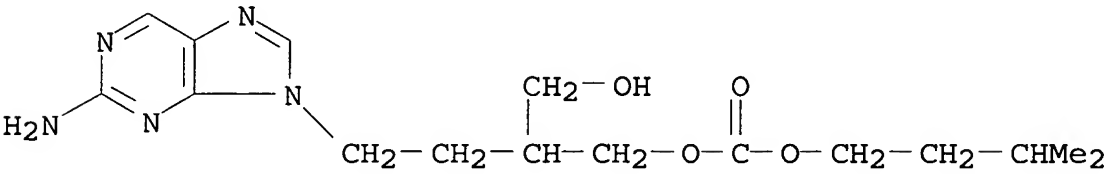


RN 213273-31-5 ZCAPLUS

CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl pentyl ester (9CI) (CA INDEX NAME)



RN 213273-32-6 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl 3-methylbutyl ester (9CI) (CA INDEX NAME)



IT **104227-97-6P 213273-25-7P 213273-26-8P**
213273-27-9P 213273-28-0P 213273-30-4P
213273-31-5P 213273-32-6P
(synthesis and evaluation of 2-amino-9-(3-hydroxymethyl-4-alkoxycarbonyloxybut-1-yl)purines as potential prodrugs of penciclovir)

L34 ANSWER 25 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1997:542449 Document No. 127:210347 Pharmaceutical compositions containing famciclovir monohydrate. Campbell, Kenneth Churchill; Greenway, Michael John; Hancock, Stephen Andrew (Smithkline Beecham PLC, UK). PCT Int. Appl. WO 9729108 A1 **19970814**, 9 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-EP523 19970204. PRIORITY: GB 1996-2403 19960207; GB 1996-18494 19960905.

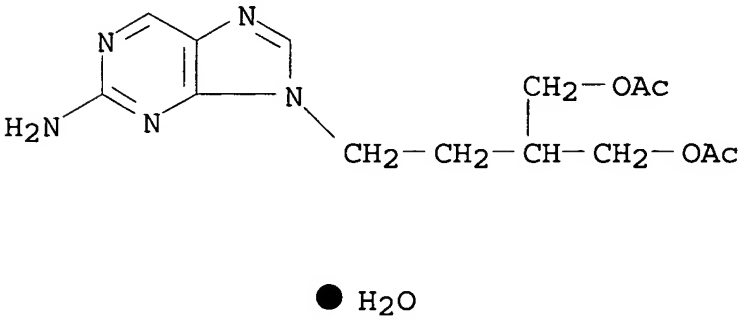
AB A process for the prepn. of famciclovir (I) monohydrate by exposing the anhyd. form to an atm. contg. a high concn. of water vapor and pharmaceutical formulations contg. I monohydrate are disclosed. Thus, 150 g I was dissolved in hot water and the hot soln. was

allowed to cool slowly to 5.degree. with continuous stirring for 3 h. The monohydrate crystals were filtered and then dried by allowing the excess water to evap. under ambient condition for .apprx.2 days. An oral suspension contg. 35.20% I monohydrate was prepd. and stored at 25.degree. and the crystal growth was monitored and compared with a suspension contg. anhyd. I over a period of 1 wk. No crystal growth in the monohydrate suspension was obsd. while the crystals in anhydrate suspension had grown to ten times their original size, making them less pharmaceutic ally acceptable.

IT **131118-73-5P**
(pharmaceutical compns. contg. famciclovir monohydrate)

RN 131118-73-5 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, diacetate (ester), monohydrate (9CI) (CA INDEX NAME)



IT **131118-73-5P**
(pharmaceutical compns. contg. famciclovir monohydrate)

L34 ANSWER 26 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

1997:494380 Document No. 127:201933 In vitro oxidation of famciclovir and 6-deoxypenciclovir by aldehyde oxidase from human, guinea pig, rabbit, and rat liver. Rashidi, Mohammad R.; Smith, John A.; Clarke, Stephen E.; Beedham, Christine (School of Pharmacy, Pharmaceutical Chemistry, University of Bradford, Bradford, BD7 1 DP, UK). Drug Metabolism and Disposition, 25(7), 805-813 (English) **1997.** CODEN: DMDSAI. ISSN: 0090-9556. Publisher: Williams & Wilkins.

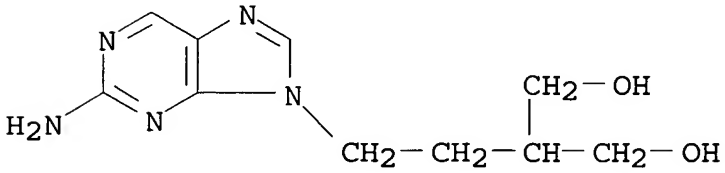
AB Famciclovir, a 9-substituted guanine deriv., is a new antiviral agent which undergoes rapid hydrolysis and oxidn. in man to yield the active antiherpes agent, penciclovir. Studies with human liver cytosol have indicated that the oxidn. of the penultimate metabolite, 6-deoxypenciclovir, to penciclovir is catalyzed by the molybdenum hydroxylase, aldehyde oxidase. In the present study the oxidn. of famciclovir and 6-deoxypenciclovir with partially purified molybdenum hydroxylases from human, guinea pig, rabbit, and rat

livers and bovine milk xanthine oxidase has been investigated. Famciclovir and 6-deoxypenciclovir were oxidized predominantly to 6-oxo-famciclovir and penciclovir, resp., by human, guinea pig, and rat liver aldehyde oxidase. Small amts. of 8-oxo and 6,8-dioxo-metabolites were also formed from each substrate. Famciclovir and 6-deoxypenciclovir were good substrates for rabbit liver aldehyde oxidase but, in each case, two major metabolites were formed. 6-Deoxypenciclovir was converted to penciclovir and 8-oxo-6-deoxypenciclovir in approx. equal quantities; famciclovir was oxidized to 6-oxo-famciclovir and a second metabolite which, on the basis of chromatog. and UV spectral data, was thought to be 8-oxo-famciclovir. Two groups of Sprague Dawley rats were identified; those contg. hepatic aldehyde oxidase and xanthine oxidase and those with only xanthine oxidase. These have been designated AO-active and AO-inactive rats, resp. Famciclovir was not oxidized by enzyme from AO-inactive rats or bovine milk xanthine oxidase although 6-deoxypenciclovir was slowly converted to penciclovir by rat liver or milk xanthine oxidase. Inhibitor studies showed in human, guinea pig, and rabbit liver that xanthine oxidase did not contribute to the oxidn. of famciclovir and 6-deoxypenciclovir; thus it is proposed that drug activation in vivo would be catalyzed solely by aldehyde oxidase.

IT **104227-86-3**
(in vitro oxidn. of famciclovir and 6-deoxypenciclovir by aldehyde oxidase from human, guinea pig, rabbit, and rat liver)

RN 104227-86-3 ZCAPLUS

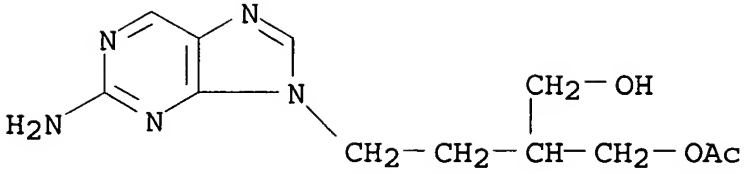
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



IT **104227-88-5**
(in vitro oxidn. of famciclovir and 6-deoxypenciclovir by aldehyde oxidase from human, guinea pig, rabbit, and rat liver)

RN 104227-88-5 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monoacetate (ester) (9CI) (CA INDEX NAME)



IT **104227-86-3**
(in vitro oxidn. of famciclovir and 6-deoxypenciclovir by aldehyde oxidase from human, guinea pig, rabbit, and rat liver)

IT **104227-88-5**
(in vitro oxidn. of famciclovir and 6-deoxypenciclovir by aldehyde oxidase from human, guinea pig, rabbit, and rat liver)

L34 ANSWER 27 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

1996:662406 Document No. 125:292232 Pharmacokinetics of famciclovir. Absorption, distribution, metabolism and excretion in rats and dogs. Filer, Colin W.; Ramji, Jayant; Takahashi, Naoki; Yasuda, Eiichi; Kumakura, Hiroyuki; Nishioka, Yoshitaka (SmithKline Beecham Pharmaceuticals, UK). Yakuri to Chiryo, 24(8), 1805-1829 (Japanese) **1996.** CODEN: YACHDS. ISSN: 0386-3603. Publisher: Raifu Saiensu Shuppan K.K..

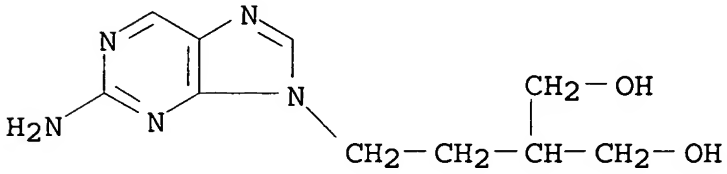
AB When 14C-famiciclovir was administered orally to rats, the results suggested a redn. of the absorption rate and a delay in elimination at high doses (4000 mg.kg). In the dog, plasma radioactivity was increased as the dose increased. In the rat and dog, penciclovir and its precursor, BRL 42359, were predominant in plasma and urine. The results, however, suggested that the rate of oxidn. of BRL 42359 to penciclovir was decreased at high doses (4000 mg/kg in the rat and 250 mg/kg in the dog). In the rat, about 60% of the orally administered radioactivity was excreted in the urine and about 40% in the feces, while in the dog, about 90% was excreted in the urine and about 10% in the feces. Absorption, metab. and excretion of famciclovir were unaffected by repeat dosing. Famciclovir had no effect on drug metabolizing enzymes in the rat liver. In vitro protein binding rates in rat and dog plasma were 10.8 to 23.9% for the major metabolite of famciclovir, penciclovir, and 5.6 to 20.2% for its precursor, BRL 42359. When 14C-famciclovir was administered orally to rats, radioactivity was distributed and eliminated rapidly. After repeat oral dosing, there was no evidence of accumulation in any organ or tissue except in the fur. When 14C-famciclovir was administered orally to pregnant rats, the concns. of radioactivity in fetuses were lower than those in the maternal blood and radioactivity was not detected at 24 h after dosing. When 14C-famciclovir was administered orally to lactating rats, the peak concns. of radioactivity in milk were obsd. at 0.5 and 2 h after dosing. The concns. of radioactivity in milk were

always higher than those in plasma, but fell to below the limit of reliable detn. by 24 h after dosing. The majority of the radioactivity was found to be penciclovir.

IT **104227-86-3**, BRL 42359
(pharmacokinetics of famciclovir in rats and dogs)

RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



IT **104227-86-3**, BRL 42359
(pharmacokinetics of famciclovir in rats and dogs)

L34 ANSWER 28 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

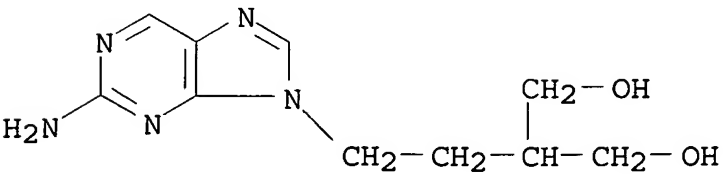
1996:278107 Document No. 125:34011 A direct approach to the synthesis of famciclovir and penciclovir. Choudary, Bernadette M.; Geen, Graham R.; Kincey, Peter M.; Parratt, Martin J.; Dales, J. Robert M.; Johnson, Graham P.; O'Donnell, Steven; Tudor, David W.; Woods, Neil (SmithKline Beecham Pharmaceuticals, Harlow, CM19 5AW, UK). Nucleosides & Nucleotides, 15(5), 981-994 (English) **1996.** CODEN: NUNUD5. ISSN: 0732-8311. Publisher: Dekker.

AB Reaction of 2-amino-6-chloropurine with tri-Et 3-bromopropane-1,1,1-tricarboxylate followed by decarbethoxylation/transesterification of the unpurified product was the key sequence in synthesizing both the anti-herpesvirus agent penciclovir and its oral form famciclovir in three isolated steps.

IT **104227-86-3P**
(prepn. of famciclovir and penciclovir)

RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



IT **104227-86-3P**

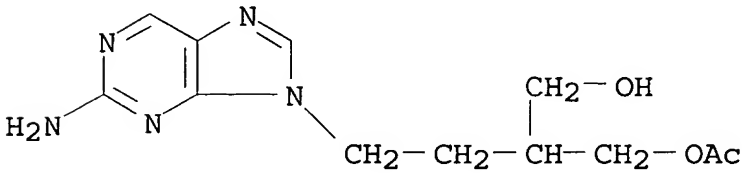
(prepn. of famciclovir and penciclovir)

L34 ANSWER 29 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1996:58810 Document No. 124:185764 Determination of liquid chromatographic peak purity by electrospray ionization mass spectrometry. Bryant, Duncan K.; Kingswood, Michael D.; Belenguer, Ana (Tonbridge Kent, TN11 9AN, UK). Journal of Chromatography, A, 721(1), 41-51 (English) **1996.** CODEN: JCRAEY. ISSN: 0021-9673. Publisher: Elsevier.

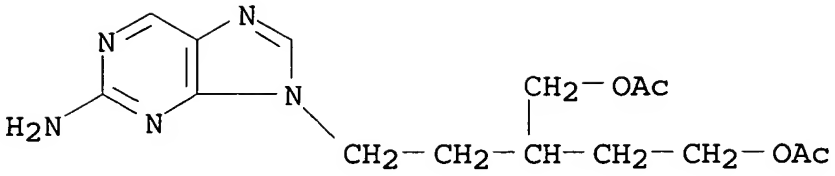
AB A technique is described whereby the purity of an HPLC peak can be detd. using electrospray liq. chromatog.-electrospray ionization mass spectrometry. Electrospray mass spectra acquired across an HPLC peak are summed and examd. for co-eluting impurities. The mass spectrometer is set up to produce solely cationic mols. and background noise is minimized so that minor coeluting impurities can be obsd. down to a level of <0.1% of the major component. This method offers advantages over using diode-array UV detection (LC-DAD) for the detn. of HPLC peak purity, namely components with similar UV spectra can be distinguished, the mol. wt. of the impurity can be detd. and structural data can be obtained by using tandem mass spectrometry. The effectiveness of the technique was demonstrated with substances of pharmaceutical interest which were chromatographed on an HPLC system designed to intentionally co-elute a no. of impurity stds. with these compds.

IT **104227-88-5**, BRL 43594 **174155-69-2**, BRL 55842
(detn. of HPLC peak purity by electrospray ionization mass spectrometry)

RN 104227-88-5 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monoacetate (ester) (9CI) (CA INDEX NAME)



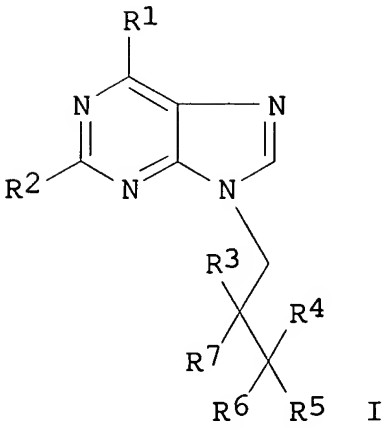
RN 174155-69-2 ZCAPLUS
CN 1,4-Butanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, diacetate (ester) (9CI) (CA INDEX NAME)



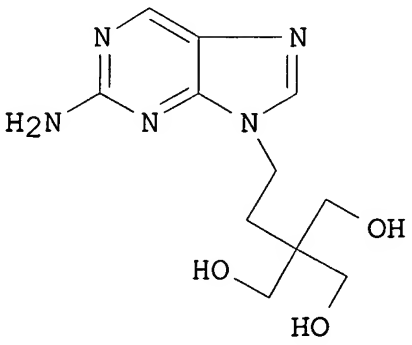
IT **104227-88-5**, BRL 43594 **174155-69-2**, BRL 55842
(detn. of HPLC peak purity by electrospray ionization mass spectrometry)

L34 ANSWER 30 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1995:994374 Document No. 124:202289 Preparation of purine-substituted hepadnaviridae antiviral agents. Marcuccio, Sebastian Mario; Holan, George; Coghlan, Phillip Albert; Jarvis, Karen Elizabeth; Robertson, Alan Duncan; Turner, Kathleen Anne; Weigold, Helmut (Commonwealth Scientific and Industrial Research Organisation, Australia). PCT Int. Appl. WO 9522330 A1 **19950824**, 183 pp. DESIGNATED STATES: W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UG; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1995-AU76 19950217. PRIORITY: AU 1994-3934 19940217; AU 1994-320 19941223.

GI



I



II

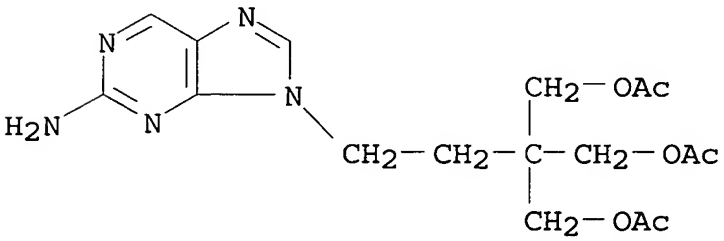
AB The title compds. [I; R1 = hydrogen, halogen, hydroxy, azide, (un)substituted alkyl, (un)substituted aryloxy, mercapto, etc.; R2 = hydrogen, hydroxy, azide, (un)substituted alkoxy, (un)substituted

aryloxy, mercapto, (un)substituted amino, etc.; R3, R7 = hydrogen, (un)substituted alkyl, halogen, hydroxy, azide, (un)substituted alkoxy, (un)substituted aryloxy, mercapto, (un)substituted thio, (un)substituted amino; R3R7 = :O, :S, :NOH, etc.; R5, R6 = (un)substituted alkyl, halogen, hydroxy, azide, (un)substituted alkoxy, (un)substituted aryloxy, mercapto, etc.; etc.], useful as hepadnaviridae-active antiviral agents, are prepd. and I-contg. formulations presented. Thus, purine deriv. II (m.p. 190-191.degree.) was prepd. from 9-[4-acetoxy-3,3-bis(acetoxymethyl)but-1-yl]-2-aminopurine and demonstrated a EC50 against human hepatitis B virus of 0.16 .mu.M.

IT **172645-08-8P 172645-19-1P 172645-20-4P**
172645-24-8P 172645-25-9P 172645-46-4P
172645-47-5P 172645-53-3P 172645-55-5P
172645-58-8P 172645-59-9P 172645-63-5P
172645-66-8P 172645-67-9P 172645-68-0P
172645-69-1P 172645-77-1P 172645-78-2P
172645-79-3P 172645-81-7P 172645-82-8P
172645-83-9P 172646-02-5P 172646-04-7P
(prepn. of purine-substituted hepadnaviridae antiviral agents)

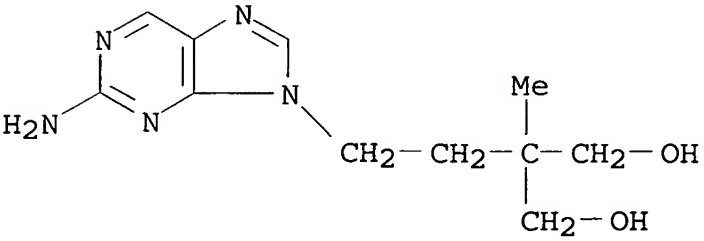
RN 172645-08-8 ZCAPLUS

CN 1,3-Propanediol, 2-[(acetyloxy)methyl]-2-[2-(2-amino-9H-purin-9-yl)ethyl]-, diacetate (ester) (9CI) (CA INDEX NAME)

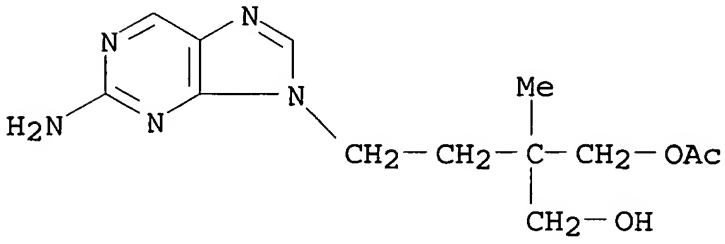


RN 172645-19-1 ZCAPLUS

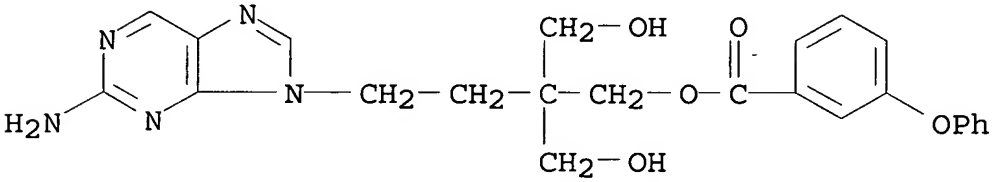
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-2-methyl- (9CI) (CA INDEX NAME)



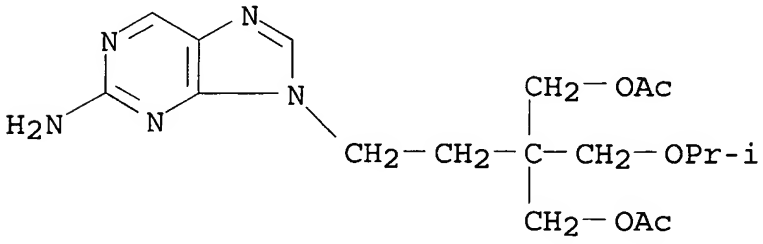
RN 172645-20-4 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-2-methyl-, monoacetate (ester) (9CI) (CA INDEX NAME)



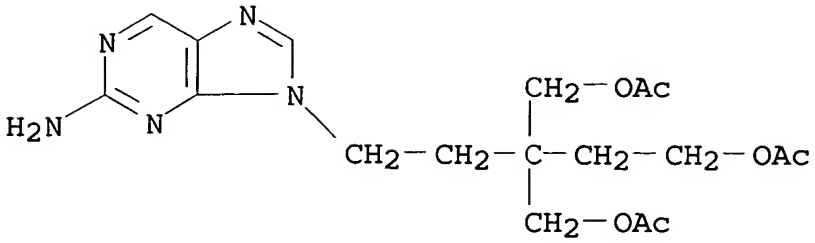
RN 172645-24-8 ZCAPLUS
CN Benzoic acid, 3-phenoxy-, 4-(2-amino-9H-purin-9-yl)-2,2-bis(hydroxymethyl)butyl ester (9CI) (CA INDEX NAME)



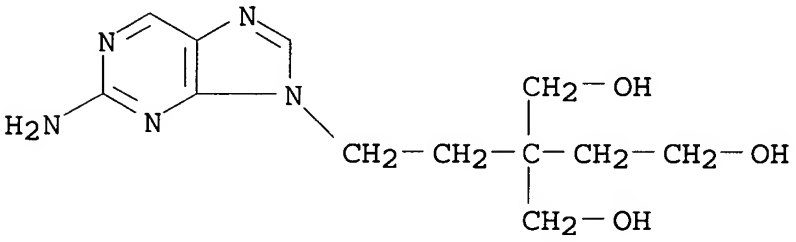
RN 172645-25-9 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-2-[(1-methylethoxy)methyl]-, diacetate (ester) (9CI) (CA INDEX NAME)



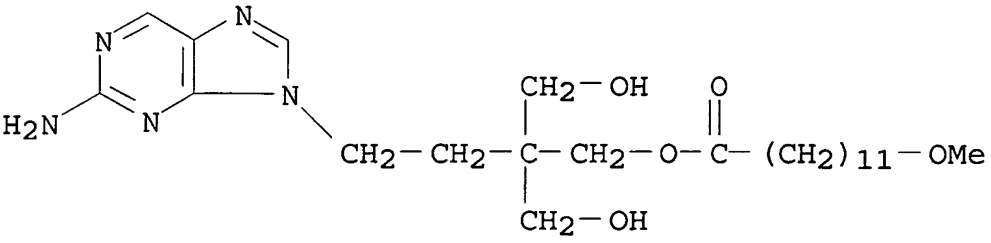
RN 172645-46-4 ZCAPLUS
CN 1,4-Butanediol, 2-[(acetyloxy)methyl]-2-[2-(2-amino-9H-purin-9-yl)ethyl]-, diacetate (ester) (9CI) (CA INDEX NAME)



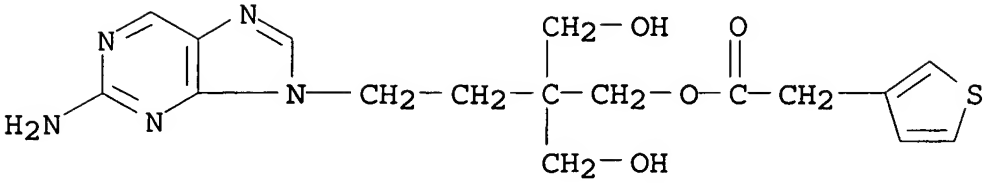
RN 172645-47-5 ZCAPLUS
CN 1,4-Butanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-2-(hydroxymethyl)-
(9CI) (CA INDEX NAME)



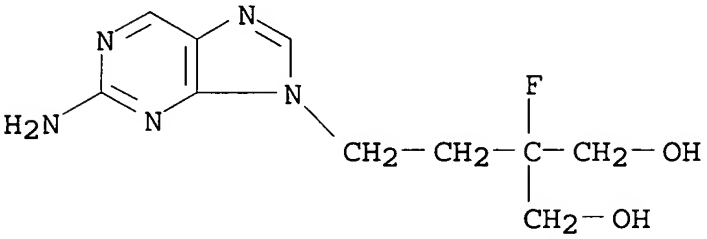
RN 172645-53-3 ZCAPLUS
CN Dodecanoic acid, 12-methoxy-, 4-(2-amino-9H-purin-9-yl)-2,2-
bis(hydroxymethyl)butyl ester (9CI) (CA INDEX NAME)



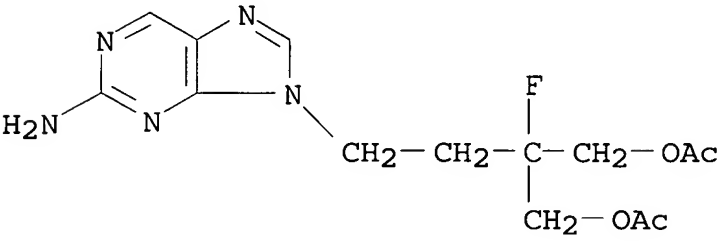
RN 172645-55-5 ZCAPLUS
CN 3-Thiopheneacetic acid, 4-(2-amino-9H-purin-9-yl)-2,2-
bis(hydroxymethyl)butyl ester (9CI) (CA INDEX NAME)



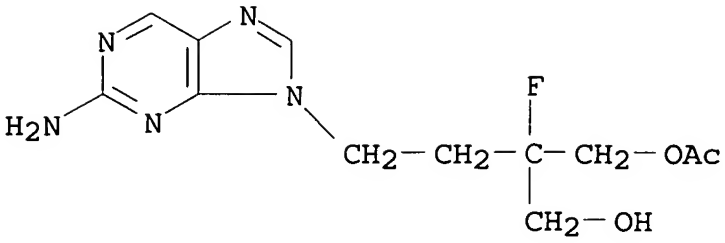
RN 172645-58-8 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-2-fluoro- (9CI) (CA INDEX NAME)



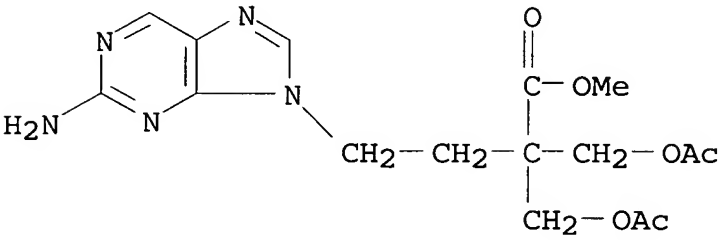
RN 172645-59-9 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-2-fluoro-, diacetate (ester) (9CI) (CA INDEX NAME)



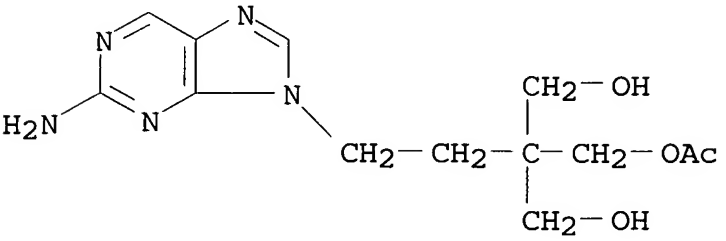
RN 172645-63-5 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-2-fluoro-, monoacetate (ester) (9CI) (CA INDEX NAME)



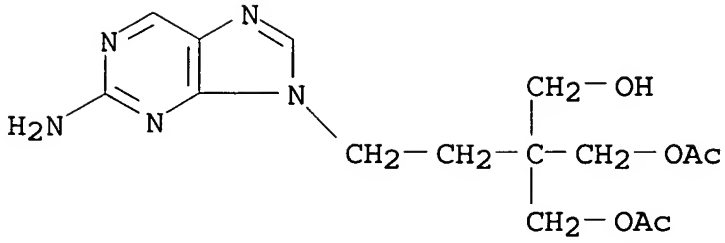
RN 172645-66-8 ZCAPLUS
CN 9H-Purine-9-butanoic acid, .alpha.,.alpha.-bis[(acetyloxy)methyl]-2-amino-, methyl ester (9CI) (CA INDEX NAME)



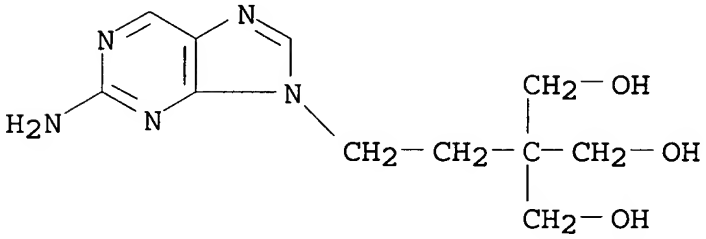
RN 172645-67-9 ZCAPLUS
CN 1,3-Propanediol, 2-[(acetyloxy)methyl]-2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



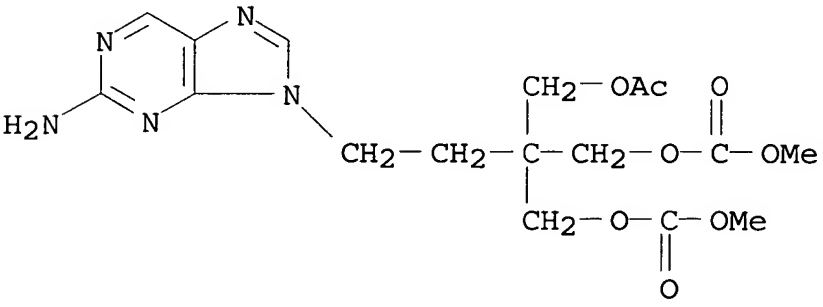
RN 172645-68-0 ZCAPLUS
CN 1,3-Propanediol, 2-[(acetyloxy)methyl]-2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monoacetate (ester) (9CI) (CA INDEX NAME)



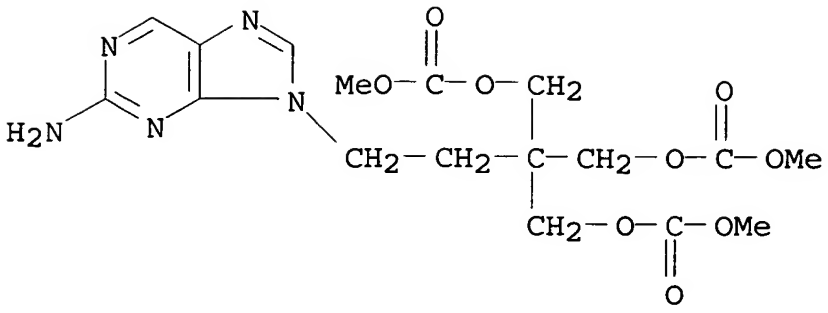
RN 172645-69-1 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-2-(hydroxymethyl)- (9CI) (CA INDEX NAME)



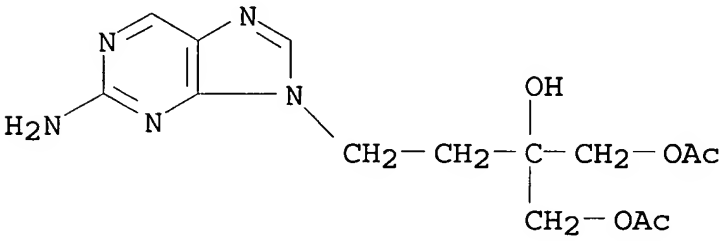
RN 172645-77-1 ZCAPLUS
CN Carbonic acid, 2-[(acetyloxy)methyl]-2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediyl dimethyl ester (9CI) (CA INDEX NAME)



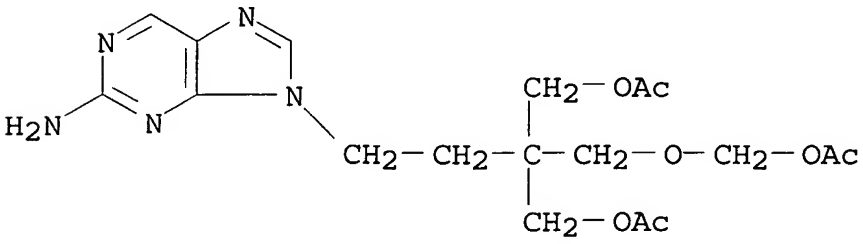
RN 172645-78-2 ZCAPLUS
CN Carbonic acid, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-2-[[(methoxycarbonyl)oxy]methyl]-1,3-propanediyl dimethyl ester (9CI) (CA INDEX NAME)



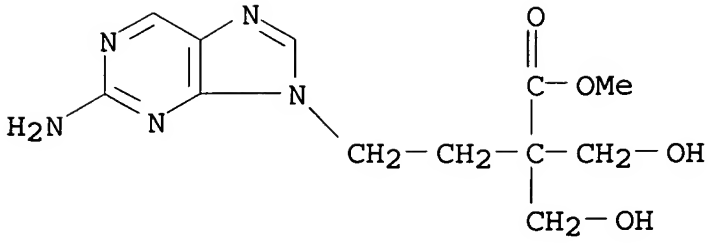
RN 172645-79-3 ZCAPLUS
CN 1,2,3-Propanetriol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, 1,3-diacetate (9CI) (CA INDEX NAME)



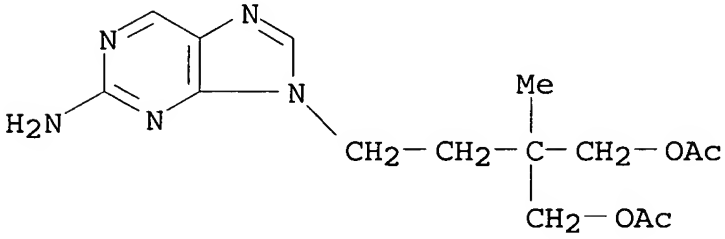
RN 172645-81-7 ZCAPLUS
CN 1,3-Propanediol, 2-[[(acetyloxy)methoxy]methyl]-2-[2-(2-amino-9H-purin-9-yl)ethyl]-, diacetate (ester) (9CI) (CA INDEX NAME)



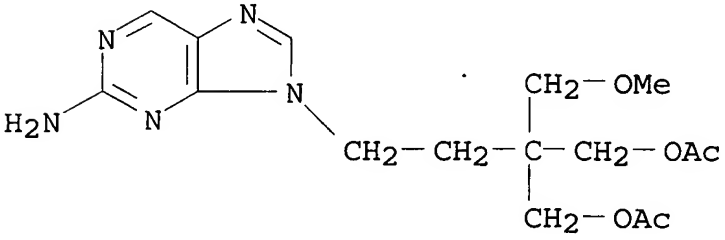
RN 172645-82-8 ZCAPLUS
CN 9H-Purine-9-butanoic acid, 2-amino-.alpha.,.alpha.-bis(hydroxymethyl)-, methyl ester (9CI) (CA INDEX NAME)



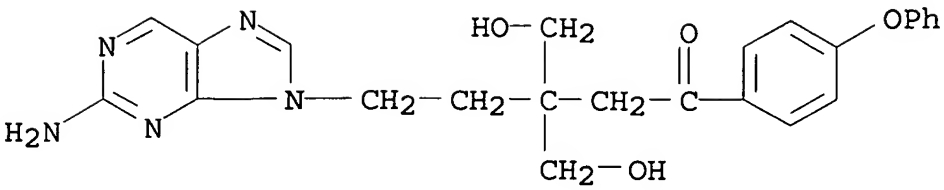
RN 172645-83-9 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-2-methyl-, diacetate (ester) (9CI) (CA INDEX NAME)



RN 172646-02-5 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-2-(methoxymethyl)-, diacetate (ester) (9CI) (CA INDEX NAME)



RN 172646-04-7 ZCAPLUS
CN 1-Pentanone, 5-(2-amino-9H-purin-9-yl)-3,3-bis(hydroxymethyl)-1-(4-phenoxyphenyl)- (9CI) (CA INDEX NAME)



IT **172645-08-8P 172645-19-1P 172645-20-4P**
172645-24-8P 172645-25-9P 172645-46-4P
172645-47-5P 172645-53-3P 172645-55-5P
172645-58-8P 172645-59-9P 172645-63-5P
172645-66-8P 172645-67-9P 172645-68-0P
172645-69-1P 172645-77-1P 172645-78-2P
172645-79-3P 172645-81-7P 172645-82-8P
172645-83-9P 172646-02-5P 172646-04-7P
(prepn. of purine-substituted hepadnaviridae antiviral agents)

L34 ANSWER 31 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1995:654036 Document No. 123:101950 Metabolic and pharmacokinetic studies following oral administration of famciclovir to the rat and dog. Filer, C. W.; Ramji, J. V.; Allen, G. D.; Brown, T. A.; Fowles, S. E.; Hollis, F. J.; Mort, E. E. (Drug Metabolism Pharmacokinetics Department, SmithKline Beecham Pharmaceuticals, Welwyn, AL6 9AR, UK). Xenobiotica, 25(5), 477-90 (English) **1995.** CODEN: XENOBH. ISSN: 0049-8254. Publisher: Taylor & Francis.

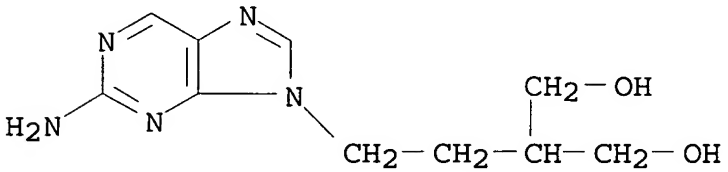
AB Drug-related material was well absorbed following oral administration of 14C-famciclovir to the male rat at doses up to 4000 mg/kg and to the male dog at doses up to 250 mg/kg, as judged by the early onset of the peak blood or plasma concns. of radioactivity (usually .ltoreq.1.5 h) and the rapid and extensive excretion of radioactivity in the urine (57-76 and 86-89% of dose in rat and dog resp.). Famciclovir underwent extensive first-pass metab. in both species. In rat, following dosing at 40 mg/kg, famciclovir was rapidly and extensively metabolized to the active antiviral compd. penciclovir, which reached peak concns. in the plasma (mean 3-5 .mu.g/mL) at 0.5 h. The 6-deoxy precursor of penciclovir, BRL 42359, was the only other major metabolite detected in rat plasma. Cmax values for BRL 42359 (mean 2.2 .mu.g/mL) were also achieved at 0.5 h. In dog, extensive conversion of famciclovir to penciclovir, via BRL 42359, also occurred, but its rate of formation from BRL 42359 was somewhat slower than in rat. In dog, following dosing at 25 mg/kg, Cmax values for penciclovir (mean 4.4 .mu.g/mL) occurred at 3 h and were lower than the Cmax values for BRL 42359 (mean 10.0 .mu.g/mL) which were achieved at 1 h. A dose-dependent decrease in the conversion of BRL 42359 to

penciclovir occurred in both species, resulting in changes in the ratios of the plasma concns. of the two metabolites with increasing dose. In rat, the urinary excretion of penciclovir decreased from 36% of dose at 40 mg/kg to 21% at 4000 mg/kg, and was accompanied by a corresponding increase in the urinary excretion of BRL 42359. In dog, a similar decrease in the urinary excretion of penciclovir occurred on increasing the dose of famciclovir from 25 to 250 mg/kg. Penciclovir and BRL 42359 were the major metabolites detected in urine and feces. In rat, following dosing at 40 mg/kg, 54 and 22% of dose were recovered in the excreta as penciclovir and BRL 42359, resp. Corresponding recoveries of the two metabolites in the dog were 34 and 50% of dose. The metabolic fate of famciclovir in these animal species is, therefore, similar to that reported previously in man.

IT **104227-86-3**, BRL 42359 **104227-88-5**, BRL 43594
(famciclovir metab. and pharmacokinetics studies after oral administration to rat and dog)

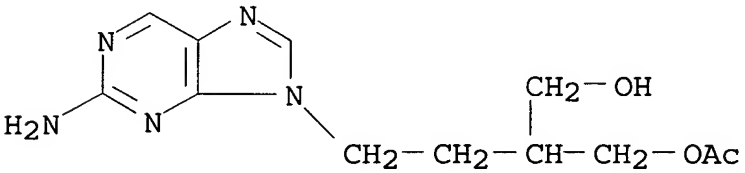
RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



RN 104227-88-5 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monoacetate (ester) (9CI) (CA INDEX NAME)



IT **104227-86-3**, BRL 42359 **104227-88-5**, BRL 43594
(famciclovir metab. and pharmacokinetics studies after oral administration to rat and dog)

L34 ANSWER 32 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

1995:371955 Document No. 122:150794 Role of aldehyde oxidase in the in vitro conversion of famciclovir to penciclovir in human liver.

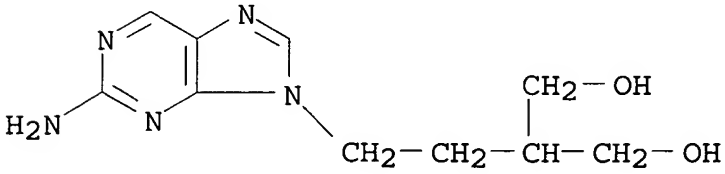
Clarke, Stephen E.; Harrell, Andrew W.; Chenery, Richard J. (Dep. of Drug Metabolism and Pharmacokinetics, SmithKline Beecham Pharmaceuticals, UK). Drug Metabolism and Disposition, 23(2), 251-4 (English) **1995.** CODEN: DMDSAI. ISSN: 0090-9556. Publisher: Williams & Wilkins.

AB Famciclovir is the diacetyl 6-deoxy deriv. of the active antiviral penciclovir that is for use in the treatment of infections caused by the herpes family of viruses. The major pathway of conversion is via d-deacetylation to BRL 42359, followed by oxidn. to pencilovir. On oral dosing of famciclovir to humans, only penciclovir and BRL 42359 can be detected consistently in the plasma; thus, attention was focused on the oxidn. reaction. This 6-oxidn. occurred rapidly in human liver cytosol, had no requirement for cofactors, and followed simple Michaelis-Menten kinetics with a KM of 115 .mu.M .+-. 23 (N = 3). Using inhibitors of xanthine oxidase (allopurinol) and aldehyde oxidase (menadione and isovanillin), the relative roles of these enzymes in this process were detd. At a concn. of BRL 42359 that reflected plasma concns. obsd. in human (4 .mu.M), both menadione (IC50 7 .mu.M) and isovanillin (IC50 15 .mu.M) caused extensive inhibition of the 6-oxidn. reaction. In contrast, allopurinol caused no significant inhibition, confirming earlier in vivo work. At higher substrate concns. (50 and 200 .mu.M), the results with these inhibitors were broadly similar. These results provide strong evidence that aldehyde oxidase and not xanthine oxidase is responsible for the 6-oxidn. of BRL 42359 to penciclovir in human liver cytosol, and this is likely to reflect the in vivo situation.

IT **104227-86-3**, BRL 42359
(aldehyde oxidase in oxidn. to penciclovir in human liver)

RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



IT **104227-86-3**, BRL 42359
(aldehyde oxidase in oxidn. to penciclovir in human liver)

L34 ANSWER 33 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

1994:400195 Document No. 121:195 Metabolic and pharmacokinetic studies following oral administration of 14C-famciclovir to healthy subjects. Filer, C. W.; Allen, G. D.; Brown, T. A.; Fowles, S. E.;

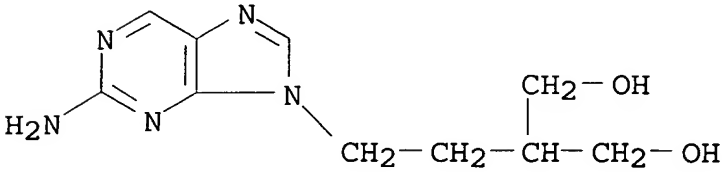
Hollis, F. J.; Mort, E. E.; Prince, W. T.; Ramji, J. V. (Drug Metab. Pharmacokinet. Dep., SmithKline Beecham Pharm., Frythe/Welwyn/Herts, AL6 9AR, UK). Xenobiotica, 24(4), 357-68 (English) **1994.** CODEN: XENOBH. ISSN: 0049-8254.

AB Following oral administration of 14C-famciclovir (500 mg) to three healthy male subjects, drug-related material was rapidly absorbed as judged by peak plasma concns. of radioactive material being achieved by 0.75 h (6.7 to 0.9 .mu.g equiv./mL (mean .+-. SD)). Famciclovir underwent extensive first-pass metab. and was only detected in the plasma of one subject at low concns. (0.5 .mu.g/mL). Famciclovir was rapidly and extensively metabolized to the active antiviral compd. penciclovir, which reached peak concns. in the plasma of 3.6 .+-. 0.7 .mu.g/mL (0.75 h). The plasma elimination half-life value for penciclovir was 2.1 .+-. 0.1 H. The 6-deoxy precursor of penciclovir, BRL 42359, was the only other relatively major metabolite detected in plasma. Peak plasma concns. of BRL 42359 (1.0 .+-. 0.1 .mu.g/mL) were achieved at 0.5 h. After 3 days, 73.0 .+-. 6.1% of the radioactive dose was excreted in urine, showing that good absorption of drug-related material occurred. Renal excretion was rapid since 60.2 .+-. 4.2 and 72.3 .+-. 5.7% of the dose was recovered in the urine samples collected up to 6 and 24 h, resp. A good recovery of the administered radioactive dose was obtained since a further 26.6 .+-. 5.1% of the dose was excreted in the feces over a 72-h period. Penciclovir and BRL 42359 were the major metabolites detected in urine and feces. Penciclovir accounted for 59.2 .+-. 4.9 and 4.2 .+-. 1.4% of the dose in 0-24 h urine and 0-48 h feces, resp. Corresponding values for BRL 42359 were 5.0 .+-. 0.5 and 17.0 .+-. 6.2%, resp. These metabolites were identified in the biol. samples using hplc-ms and ms-ms with thermospray ionization.

IT **104227-86-3**, BRL 42359
(formation of, as famciclovir metabolite, in humans)

RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



IT **104227-86-3**, BRL 42359
(formation of, as famciclovir metabolite, in humans)

L34 ANSWER 34 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

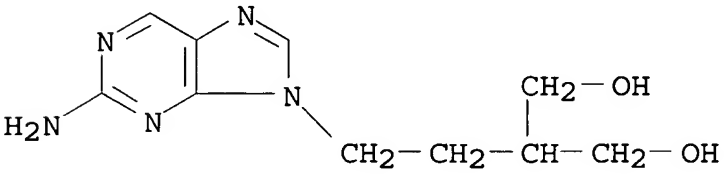
1994:260460 Document No. 120:260460 Linear pharmacokinetics of penciclovir following administration of single oral doses of famciclovir 125, 250, 500 and 750 mg to healthy volunteers. Pue, M. A.; Pratt, S. K.; Fairless, A. J.; Fowles, S.; Laroche, J.; Georgiou, P.; Prince, W. (SmithKline Beecham Pharm., The Frythe, Welwyn/Herts., AL6 9AR, UK). Journal of Antimicrobial Chemotherapy, 33(1), 119-27 (English) **1994.** CODEN: JACHDX. ISSN: 0305-7453.

AB Twenty healthy male volunteers received single oral doses of famciclovir (125-750 mg), in a randomized, single-blind, crossover study. Plasma and urine concns. of penciclovir and its 6-deoxy precursor, BRL 42359, were detd. and penciclovir plasma concn.-time data submitted to model-independent pharmacokinetic anal. Peak plasma concns. of penciclovir were obtained at median times of 0.5-0.75 h after dosing. The areas under the concn. vs. time curves (AUC) and the peak penciclovir concns. (Cmax) increased linearly with dose of famciclovir. Time to Cmax, elimination half-life, urinary recovery and renal clearance of penciclovir did not change with increasing dose. Famciclovir was excreted via the kidneys as penciclovir (60%) and BRL 42359 (5%), resp. Famciclovir was well tolerated by all subjects with a low incidence of adverse effects. In conclusion, penciclovir thus displays linear pharmacokinetics in the anticipated therapeutic dose range of famciclovir.

IT **104227-86-3**, BRL 42359
(formation of, as famciclovir metabolite, in humans)

RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)

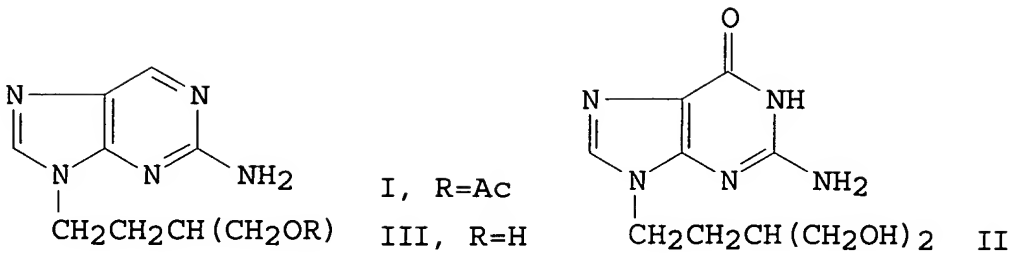


IT **104227-86-3**, BRL 42359
(formation of, as famciclovir metabolite, in humans)

L34 ANSWER 35 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

1993:160573 Document No. 118:160573 Evidence that famciclovir (BRL 42810) and its associated metabolites do not inhibit the 6.beta.-hydroxylation of testosterone in human liver microsomes. Harrell, A. W.; Wheller, S. M.; Pennick, M.; Clarke, S. E.; Chenery, R. J. (Dep. Drug Metab. Pharmacokinet., SmithKline Beecham, The Frythe/Welwyn/Herts, UK). Drug Metabolism and Disposition, 21(1), 18-23 (English) **1993.** CODEN: DMDSAI. ISSN: 0090-9556.

GI

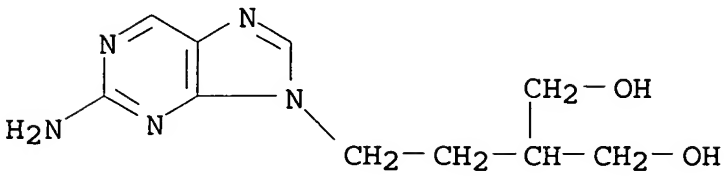


AB Famciclovir (I) is the diacetyl 6-deoxy analog of the active antiviral compd. penciclovir (II) with potential use in the treatment of infections caused by the herpes family of viruses. The major pathway of metab. of I is deacetylation to BRL 42359 (III) followed by oxidn. to II. It is possible that I may be coadministered with cyclosporin A to combat viral infections induced by immunosuppression in organ transplant and bone marrow transplant patients. As a result, information is required on possible interactions between the cytochrome P 450 3A substrate cyclosporin A and I and its metabolites in humans. In order to probe cytochrome P 450 3A activity, testosterone 6.beta.-hydroxylation in two human liver microsomal prepns. was measured. Nicardipine and ketoconazole, two drugs with known inhibitory interactions with cyclosporin A, were used as pos. controls. Profiles of 6.beta.-hydroxytestosterone prodn. showed no inhibition effected by I, II, or III when marked inhibition was obsd. in incubations contg. nicardipine, nifedipine, or ketoconazole. Further incubations of [14C]BRL 42359 with human liver cytosol and microsomes indicated that III is oxidized to II in cytosol but not in microsomes and that this reaction was not dependent on the presence of NADPH. Because P 450 resides mainly in the microsomal fraction and is dependent on the presence of cofactors for catalytic activity, it seems that this oxidn. is not catalyzed by cytochrome P 450. Evidence has, therefore, been gathered to show that I, II, and III are not inhibitors of cytochrome P 450 3A and are, therefore, unlikely to result in metabolic interactions with cyclosporin A or other P 450 3A substrates in vivo.

IT **104227-86-3**, BRL 42359
(testosterone hydroxylation by human liver microsomes response to, as famciclovir metabolite, cytochrome P 450 3A in, drug interactions in relation to)

RN 104227-86-3 ZCAPLUS

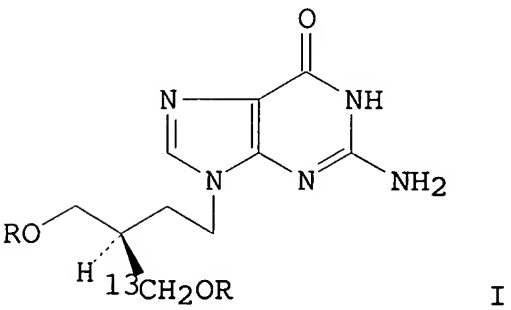
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



IT **104227-86-3**, BRL 42359
(testosterone hydroxylation by human liver microsomes response to, as famciclovir metabolite, cytochrome P 450 3A in, drug interactions in relation to)

L34 ANSWER 36 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1992:571931 Document No. 117:171931 Chemoenzymatic approach to the synthesis of the antiviral agents penciclovir and famciclovir in isotopically chiral [13C] labeled form. Sime, John T.; Barnes, Roger D.; Elson, Stephen W.; Jarvest, Richard L.; O'Toole, Kevin J. (SmithKline Beecham Pharm., Brockham Park/Betchworth/Surrey, RH3 7AJ, UK). Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (13), 1653-8 (English) **1992.** CODEN: JCPRB4. ISSN: 0300-922X. OTHER SOURCES: CASREACT 117:171931.

GI



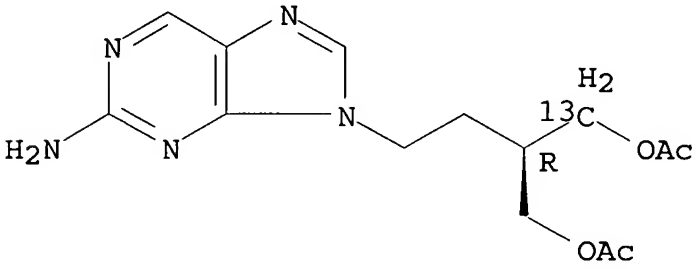
I

AB The title compds. I (R = H, Ac) were prepd. The synthesis of (+)-Me 4-benzyloxy-2-(hydroxymethyl)butanoate (II) by use of enzymic hydrolysis catalyzed by the lipase from Candida cylindracea is described as is the confirmation of the stereochem. of this intermediate as R by convergent synthetic routes. II produced by

the enzymic reaction was converted into the (-)-.alpha.-hydroxymethyl-.gamma.-butyrolactone which was compared with the (S)-(+)-.alpha.-hydroxymethyl-.gamma.-butyrolactone synthesized by an alternative, stereodefined route. The products of the enzymic reaction were used as intermediates in the synthesis of the final products.

IT **143426-34-0P**
(prepn. of)
RN 143426-34-0 ZCAPLUS
CN 1,3-Propanediol-1-13C, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, diacetate (ester), (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

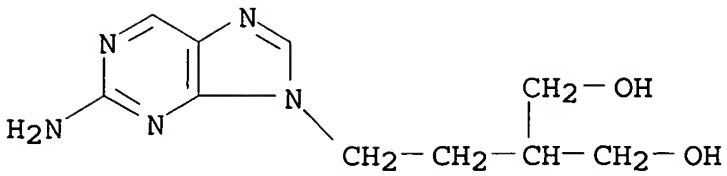


IT **143426-34-0P**
(prepn. of)

L34 ANSWER 37 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1992:462170 Document No. 117:62170 Rapid high-performance liquid chromatographic method for the analysis for the active antiherpes agent, penciclovir and its precursor, BRL 42359, in human plasma and urine following administration of the oral prodrug, famciclovir. McMeekin, Joanne R.; Fowles, Susan E.; Winton, Colin F.; Pierce, David M. (Res. Div., SmithKline Beecham Pharm., Harlow/Essex, CM19 5AD, UK). Analytical Proceedings, 29(5), 178-80 (English) **1992.** CODEN: ANPRDI. ISSN: 0144-557X.

AB This paper describes a simple HPLC method for the detn. of penciclovir (BRL 39123) and its precursor, BRL 42359, in human plasma and urine. It has been shown to be linear over the required range and accurate, precise and reproducible, generally to within 10% for both plasma and urine.

IT **104227-86-3**, BRL 42359
(detn. of, as penciclovir precursor, in blood and urine of humans by HPLC)
RN 104227-86-3 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



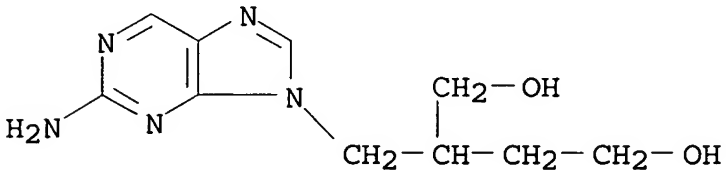
IT **104227-86-3**, BRL 42359
(detn. of, as penciclovir precursor, in blood and urine of humans by HPLC)

L34 ANSWER 38 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1992:33928 Document No. 116:33928 Antiviral activity against VZV and HSV type 1 and type 2 of the (+) and (-) enantiomers of (R,S)-9-[4-hydroxy-2-(hydroxymethyl)butyl]guanine, in comparison to other closely related acyclic nucleosides. Abele, G.; Cox, S.; Bergman, S.; Lindborg, B.; Vissgaarden, A.; Karlstroem, A.; Harmenberg, J.; Wahren, B. (Dep. Virol., Natl. Bacteriol. Lab., Stockholm, S-105 21, Swed.). Antiviral Chemistry & Chemotherapy, 2(3), 163-9 (English) **1991.** CODEN: ACCHEH. ISSN: 0956-3202.

AB The sep. (+) and (-) enantiomers of the acyclic guanosine analog 9-[4-hydroxy-2-(hydroxymethyl)butyl]guanine (2HM-HBG) were tested for inhibition of varicella-zoster virus (VZV), herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2). In all cases the (-) enantiomer was the more active enantiomer. The (+) enantiomer was 10 times less active than the racemate against VZV and inactive against HSV-1 and -2. The parent compd., 9-(4-hydroxybutyl)guanine, contg. an unbranched side chain, was inactive against VZV, whereas substitution with a hydroxymethyl group at the 2 or 3 position of the side chain conferred anti-VZV activity. The effect of hydroxymethyl substitution may increase the recognition of the compd. by the VZV thymidine kinase by increasing its similarity to the natural substrate thymidine. Further substitution of the side chain of the parent compd. with oxygen, fluorine or hydroxyl groups did not confer antiviral activity against VZV. Two VZV strains were isolated which could be grown in the presence of high concns. of 2HM-HBG and which were also cross-resistant to other nucleoside analogs. These strains induced very little viral thymidine kinase activity in infected cells and thus were probably deficient for a functional thymidine kinase. 2HM-HBG exhibited a persistent antiviral effect even after the nucleoside was removed from the medium of VZV-infected cells, whereas acyclovir did not show this effect.

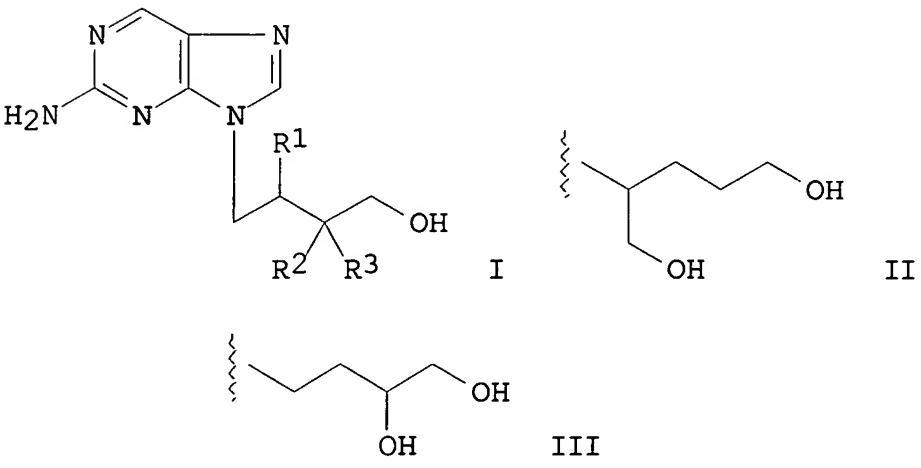
IT **104618-61-3**
(antiviral activity of, against varicella-zoster and herpes simplex viruses, structure in relation to)

RN 104618-61-3 ZCAPLUS
CN 1,4-Butanediol, 2-[(2-amino-9H-purin-9-yl)methyl]- (9CI) (CA INDEX NAME)



IT **104618-61-3**
(antiviral activity of, against varicella-zoster and herpes simplex viruses, structure in relation to)

L34 ANSWER 39 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1991:632779 Document No. 115:232779 Preparation of 2-amino-9-hydroxyalkylpurines as virucides. Johansson, Karl N. G.; Kovacs, Zsuzsanna M. I.; Lindborg, Bjoern G.; Stening, Goeran B. (Medivir AB, Swed.). U.S. US 5036071 A **19910730**, 12 pp. Cont.-in-part of U.S. Ser. No. 22,569, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1988-147051 19880122. PRIORITY: SE 1984-6538 19841221; US 1985-807853 19851211; US 1987-22569 19870309.
GI



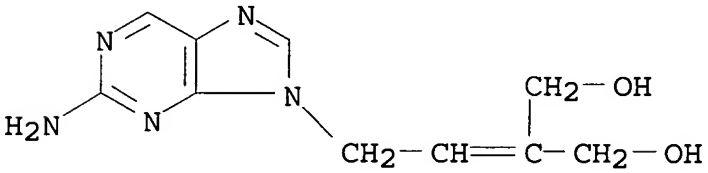
AB Title compds. (I; R1 = H, HOCH2; R2 = R1, OH; R3 = H; R1R3 = bond), were prepd. Thus, 2-amino-6-chloropurine, di-Me itaconate, and NaH

were stirred 3 d in DMF to give 66.1% di-Me 2-(2-amino-6-chloropurin-9-ylmethyl)succinate. The latter was hydrogenolyzed over Pd/C in EtOH followed by LiBH4 redn. in Me3COH to give title compd. II. Title compd. R-III at 15 mg/kg orally for 10 d in mice infected with HSV-2 strain 91075 reduced mortality at day 15 from 100% (controls) to 53%.

IT **104618-59-9P 104618-61-3P**
(prepn. of, as virucide)

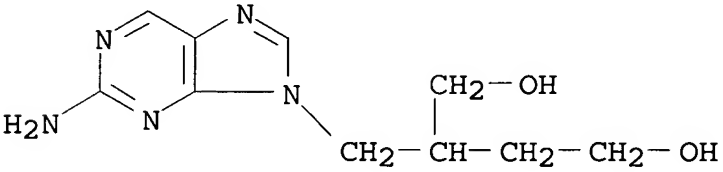
RN 104618-59-9 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethylidene]- (9CI) (CA INDEX NAME)



RN 104618-61-3 ZCAPLUS

CN 1,4-Butanediol, 2-[(2-amino-9H-purin-9-yl)methyl]- (9CI) (CA INDEX NAME)

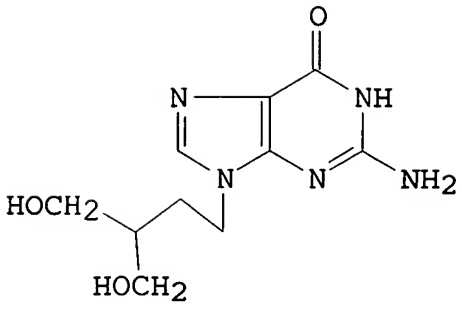


IT **104618-59-9P 104618-61-3P**
(prepn. of, as virucide)

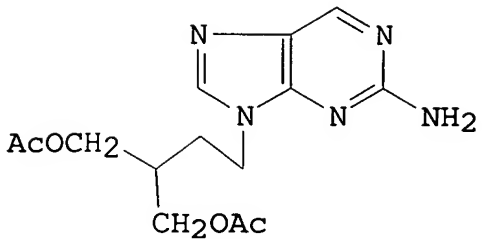
L34 ANSWER 40 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

1991:24465 Document No. 114:24465 Crystal and molecular structures of the antiviral acyclonucleoside 9-[4-hydroxy-3-(hydroxymethyl)butyl]guanine (BRL 39123, penciclovir) and its prodrug 9-[4-acetoxy-3-(acetoxymethyl)butyl]-2-aminopurine (BRL 42810, famciclovir). Harnden, Michael R.; Jarvest, Richard L.; Slawin, Alexandra M. Z.; Williams, David J. (Biosci. Res. Cent., Beecham Pharm. Res. Div., Epsom/Surrey, KT18 5XQ, UK). Nucleosides & Nucleotides, 9(4), 499-513 (English) **1990.** CODEN: NUNUD5. ISSN: 0732-8311.

GI



I



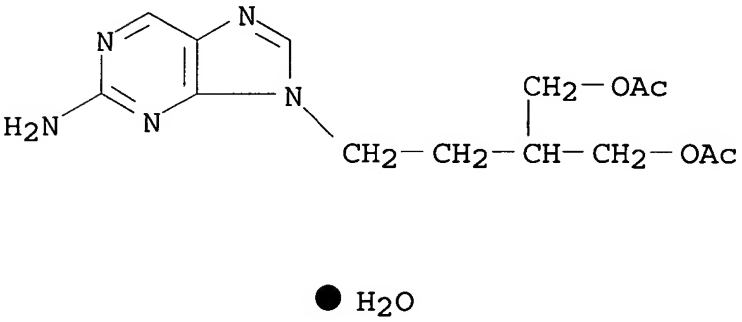
II

AB The crystal and mol. structures of acyclonucleosides related antiviral purine derivs. are reported. In I the plane of the acyclic N9 substituent is orthogonal to the purine ring, and there is an intermol. hydrogen bonds. In II characteristic changes in the geometry of the pyrimidine ring in comparison with I are obsd. In crystals of II there is an absence of major hydrogen bonding interactions and there are .pi.-.pi. interactions between parallel overlapping pyrimidine moieties.

IT **131118-73-5P**
(prepn. and crystal structure of)

RN 131118-73-5 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, diacetate (ester), monohydrate (9CI) (CA INDEX NAME)



IT **131118-73-5P**
(prepn. and crystal structure of)

L34 ANSWER 41 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

1991:64 Document No. 114:64 Assay of famciclovir and its metabolites, including the antiherpes agent penciclovir, in plasma and urine of rat, dog and man. Winton, C. F.; Fowles, S. E.; Hodge, R. A. Vere;

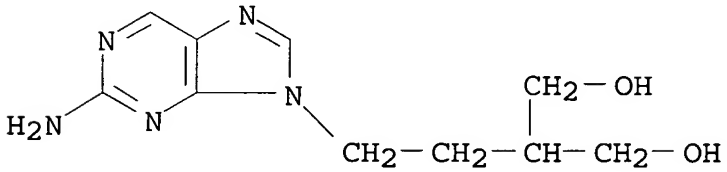
Pierce, D. M. (Res. Div., Beecham Pharm., Harlow/Essex, CM19 5AD, UK). Methodological Surveys in Biochemistry and Analysis, 20(Anal. Drugs Metab., Incl. Anti-Infect. Agents), 163-71 (English) **1990.** CODEN: MSBADU. ISSN: 0748-6715.

AB After protein pptn. with trichloroacetic acid, the compds. to be detd. were extd. by an SCX cartridge eluted with pH 11.0 phosphate buffer/MeOH. The compds. were sepd. by reversed-phase HPLC on an Apex 1 ODS 3 .mu.m column with gradient elution by pH 7.0 phosphate buffer/MeOH and UV detection with programed wavelength changes. The lower limit of sensitivity was 0.5 .mu.g/mL for plasma and, depending on the compd., 2-50 .mu.g/mL for urine. The method allows accurate and precise detn. of the pro-drug famciclovir, the antiviral agent penciclovir, and the 4 metabolites in the plasma and urine of rat, dog, and humans.

IT **104227-86-3**, BRL 42359 **104227-88-5**, BRL 43594
(detn. of, as famciclovir metabolite, in blood and urine of humans and lab. animals, by reversed-phase HPLC)

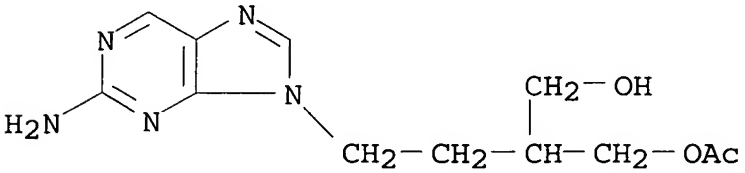
RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



RN 104227-88-5 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monoacetate (ester) (9CI) (CA INDEX NAME)



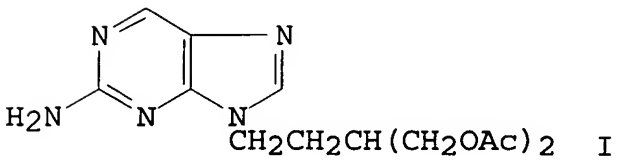
IT **104227-86-3**, BRL 42359 **104227-88-5**, BRL 43594
(detn. of, as famciclovir metabolite, in blood and urine of humans and lab. animals, by reversed-phase HPLC)

L34 ANSWER 42 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

1990:584115 Document No. 113:184115 Gradient high-performance liquid chromatographic method for the analysis of the prodrug Famciclovir

and its metabolites, including the active antiviral agent Penciclovir, in plasma and urine. Winton, Colin F.; Fowles, S. E.; Pierce, D. M.; Hodge, A. Vere (Res. Div., Beecham Pharm., Harlow/Essex, CM19 5AD, UK). Analytical Proceedings, 27(7), 181-2 (English) **1990.** CODEN: ANPRDI. ISSN: 0144-557X.

GI



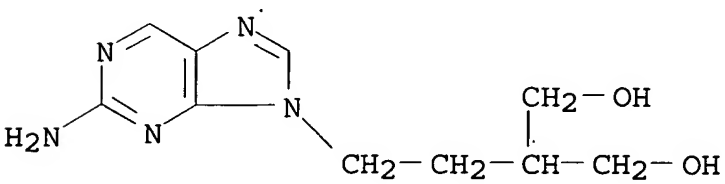
I

AB A specific HPLC method for the detn. of the prodrug Famciclovir (BRL 42810, I), its metabolites (BRL 43594, BRL 42359, BRL 39913, and BRL 42222), and the antiviral agent Penciclovir (BRL 39123) in blood plasma and urine of human and animals is presented. The method is based on an Apex 1 ODS 3-.mu.m column, MeOH-0.01M Na2HPO4 (pH 7.0) buffer (7:93 and 35:65), as the mobile phase, a flow-rate of 1-2 mL/min, and BRL 44056 as an internal std. The mean extn. efficiencies for I, Penciclovir, and metabolites are .apprx.50-60% from plasma and 70-90% from urine. Calibration graphs are linear up to 80 .mu.g/mL for all compds. in plasma with the detection limit of 0.5 .mu.g/mL. In urine, linearity is up to 2000 .mu.g/mL for Penciclovir, 1600 .mu.g/mL for BRL 42359, 200 .mu.g/mL for BRL 43594, and 40 .mu.g/mL for I and the two remaining metabolites. The detection limits in urine are 50 .mu.g/mL (Penciclovir), 40 .mu.g/mL (BRL 42359), 5 .mu.g/mL (BRL 43594), and 2 .mu.g/mL (I, BRL 42222 and BRL 39913). Coeffs. of variation within-day and between-day are <15%, and the assay is accurate to within 12%, except for the minor metabolite BRL 39913.

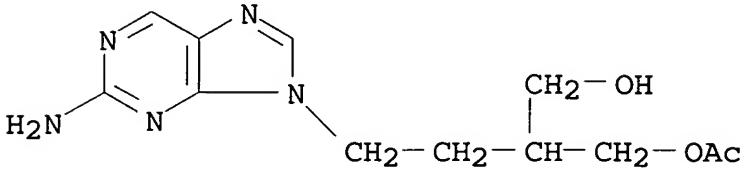
IT **104227-86-3**, BRL 42359 **104227-88-5**, BRL 43594
(detn. of, as famciclovir metabolite, in blood plasma and urine of human and lab. animals, by HPLC)

RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



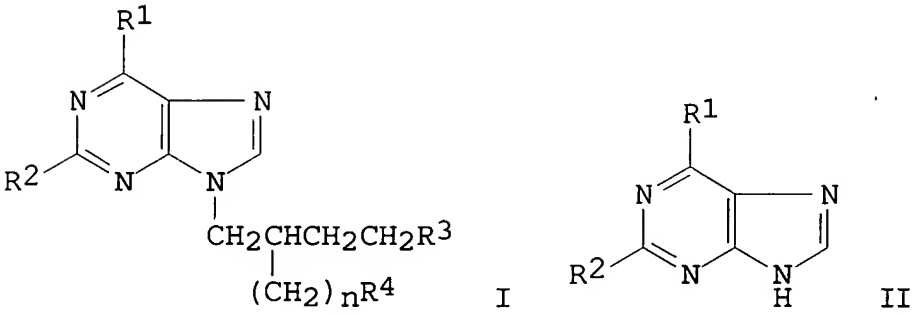
RN 104227-88-5 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monoacetate (ester) (9CI) (CA INDEX NAME)



IT **104227-86-3**, BRL 42359 **104227-88-5**, BRL 43594
(detn. of, as famciclovir metabolite, in blood plasma and urine of human and lab. animals, by HPLC)

L34 ANSWER 43 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1990:217468 Document No. 112:217468 Preparation of antiviral purine-containing nucleoside analogs. Lindborg, Bjoern Gunnar; Datema, Roelf; Johansson, Karl Nils Gunnar; Oeberg, Bo Fredrik (Medivir AB, Swed.). PCT Int. Appl. WO 8910923 A1 **19891116**, 46 pp. DESIGNATED STATES: W: AU, DK, FI, HU, JP, KR, NO, US. (English). CODEN: PIXXD2. APPLICATION: WO 1989-SE255 19890505. PRIORITY: SE 1988-1729 19880506.

GI



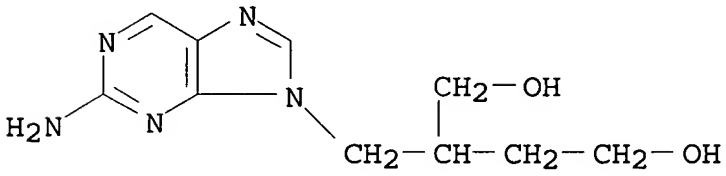
AB The title compds. [I; R1 = H, OH, SH, NH2; R2 = H, OH, F, Cl, NH2; R3 = R4 = P(O)(OM)2, P(O)(OM)CH2P(O)(OM)2, NH2, OH, etc.; or R3R4 = P(O)(OM)O; M = H, pharmaceutically acceptable counterion; n = 1, 2; other proviso apply] and their pharmaceutically acceptable salt, HIV inhibitors and hepatitis B virusinhibitor, and therefore, useful for treatment of AIDS, are prepd., e.g., by condensing purine derivs. II

with WCH2CH[(CH2)nR4]CH2CH2R3 [W = leaving group]. BrCH2CH(CH2OAc)CH2CH2OAc (prepn. given) was condensed with II (R = H, R2 = NH2) to give I [R1 = H, R2 = NH2, R3 = R4 = AcO, n = 1). In an in vitro study I (R1 = R3 = R4 = OH, R2 = NH2, n = 1) showed IC50 of 0.1-7M against HIV infection of H9 cells.

IT **104618-61-3P 126589-69-3P**
(prepn. of, as antiviral)

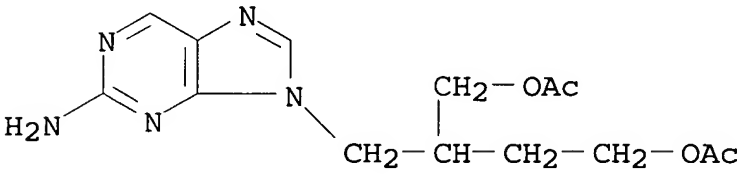
RN 104618-61-3 ZCAPLUS

CN 1,4-Butanediol, 2-[(2-amino-9H-purin-9-yl)methyl]- (9CI) (CA INDEX NAME)



RN 126589-69-3 ZCAPLUS

CN 1,4-Butanediol, 2-[(2-amino-9H-purin-9-yl)methyl]-, diacetate (ester) (9CI) (CA INDEX NAME)

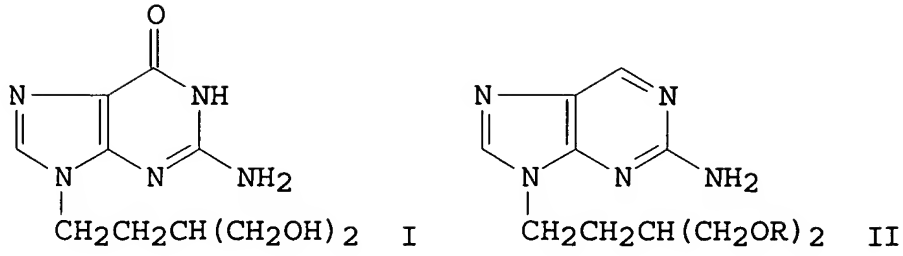


IT **104618-61-3P 126589-69-3P**
(prepn. of, as antiviral)

L34 ANSWER 44 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

1990:83948 Document No. 112:83948 Selection of an oral prodrug (BRL 42810; famciclovir) for the antiherpes virus agent BRL 39123 [9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine; penciclovir]. Hodge, R. Anthony Vere; Sutton, David; Boyd, Malcolm R.; Harnden, Michael R.; Jarvest, Richard L. (Biosci. Res. Cent., Beecham Pharm. Res. Div., Great Burgh/Epxom/Surrey, KT18 5XQ, UK). Antimicrobial Agents and Chemotherapy, 33(10), 1765-73 (English) **1989.** CODEN: AMACCQ. ISSN: 0066-4804.

GI



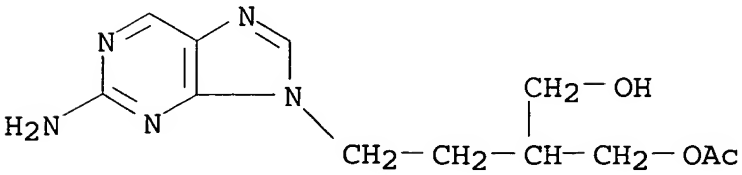
I II

AB The limited oral absorption in rodents of the antiherpes virus agent penciclovir (I) prompted a search for oral prodrugs. The I 6-deoxy deriv. [II; R = H (BRL 42359)] and the corresponding diacetyl and dipropionyl 6-deoxy derivs. (II; R = Ac (famciclovir) and R = Et CO (BRL 43599)] were tested as oral prodrugs. The in vivo absorption (dose, 0.2 mmol/kg) and the conversion to the active compd., I, were detd. in rats. Compared with the Na salt of I given i.v., the bioavailabilities of I from orally administered I, BRL 42359, famciclovir, and BRL 43599 were 1.5, 9, 41, and 27% resp. These prodrugs and 6-deoxyacyclovir were tested for stability in rat duodenal contents and for metab. in rat intestinal wall homogenate, liver homogenate, and blood and in the corresponding human fluids and tissues. Famciclovir was much more stable the BRL 43599 in human duodenal contents (half-lives, >2 h and 7 min, resp.) yet was efficiently converted to I by the tissue homogenates. The major metabolic pathway was by deacetylation followed by oxidn. at the 6 position. The rate of oxidn. was comparable to that of 6-deoxyacyclovir, which is known to be converted efficiently to acyclovir in humans. Famciclovir was selected for further evaluation and progression to studies in humans. These subsequent studies confirmed that, after oral dosing with famciclovir, more than half the dose was absorbed and rapidly converted to I.

IT **104227-88-5 125111-71-9**
(penciclovir prodrug metabolite)

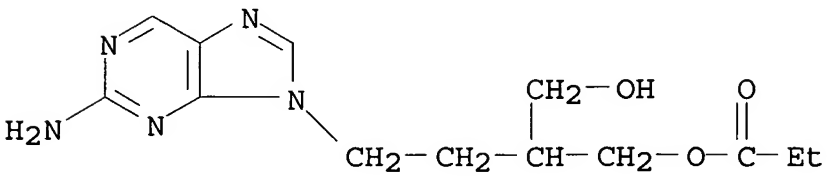
RN 104227-88-5 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monoacetate (ester) (9CI) (CA INDEX NAME)

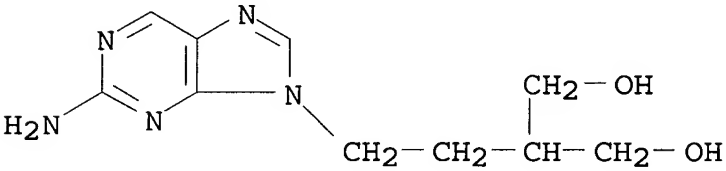


RN 125111-71-9 ZCAPLUS

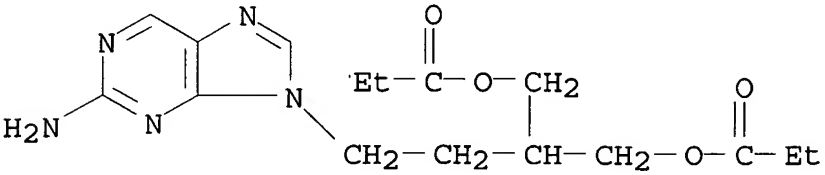
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monopropanoate (ester) (9CI) (CA INDEX NAME)



IT **104227-86-3P**, BRL 42359 **104227-90-9P**, BRL 43599
(prepn. and pharmacokinetics of, as penciclovir prodrug)
RN 104227-86-3 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



RN 104227-90-9 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, dipropanoate (ester) (9CI) (CA INDEX NAME)

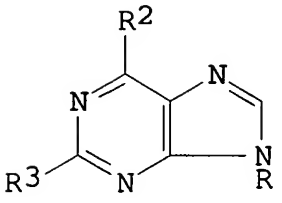


IT **104227-88-5 125111-71-9**
(penciclovir prodrug metabolite)
IT **104227-86-3P**, BRL 42359 **104227-90-9P**, BRL 43599
(prepn. and pharmacokinetics of, as penciclovir prodrug)

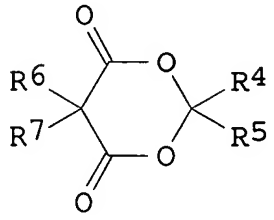
L34 ANSWER 45 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1990:7269 Document No. 112:7269 Preparation of 2-amino-9-[4-hydroxy-3-(hydroxymethyl)butyl]purines as pharmaceutical intermediates. Grinter, Trevor John; Geen, Graham Richard; Parratt, Martin John (Beecham Group PLC, UK). Eur. Pat. Appl. EP 302644 A2 **19890208**, 27 pp. DESIGNATED STATES: R: BE, CH, DE, ES, FR,

GB, IT, LI, NL. (English). CODEN: EPXXDW. APPLICATION: EP 1988-306836 19880725. PRIORITY: GB 1987-18283 19870801; GB 1988-13926 19880613.

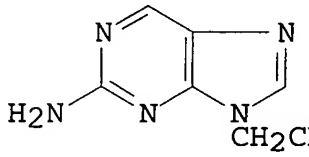
GI



I



III



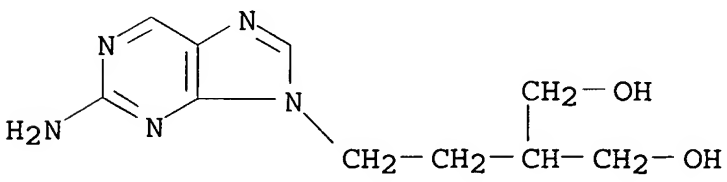
IV

AB The title compds. [I in which R = CH2CH2CH(CH2ORa)CH2ORb; Ra, Rb = H, acyl, phosphate residue; R2 = H, OH, Cl, alkoxy, phenylalkoxy; R3 = NH2] (II) were prepd., in 1 variant, by condensation of dioxaspirooctanedione III (R6R7 = CH2CH2; R4, R5 = H, alkyl, Ph; R4R5 = alkylene) with I in which R = H, followed by transesterification and redn. steps. I (R = H, R2 = Cl, R3 = NH2) was stirred overnight at 40.degree. with BrCH2CH2C(CO2Et)3 in DMF contg. K2CO3 and the N-7-alkylated product was refluxed 2 h with Pd/C in MeOH contg. HCO2NH4 to give I [R = CH2CH2C(CO2Et)3, R2 = H, R3 = NH2] which was stirred 1 h with Na in EtOH to give I [R = CH2CH2CH(CO2Et)2, R2 = H, R3 = NH2]. The latter was refluxed 1 h with NaBH4 in Me3COH with MeOH addn. to give title compd. IV.

IT **104227-86-3P**
(prepn. of, as drug intermediate)

RN 104227-86-3 ZCAPLUS

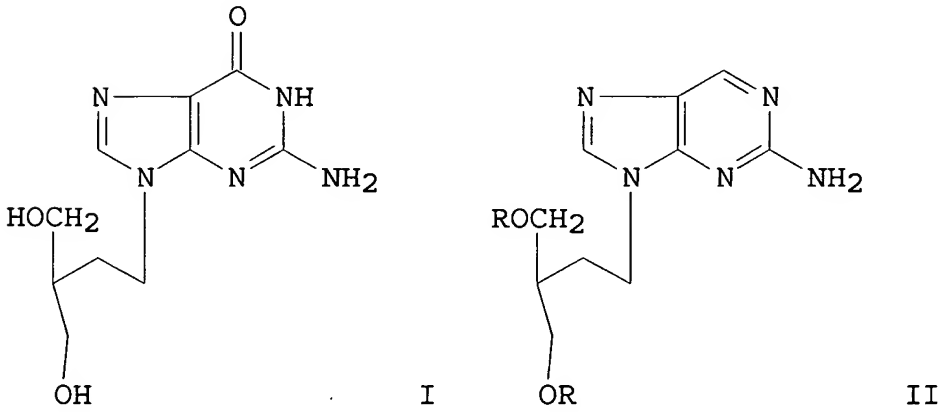
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



IT **104227-86-3P**
(prepn. of, as drug intermediate)

L34 ANSWER 46 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1989:614873 Correction of: 1989:458254 Document No. 111:214873 Correction of: 111:58254 Prodrugs of the selective antiherpesvirus agent 9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]guanine (BRL 39123) with improved gastrointestinal absorption properties. Harnden, Michael R.; Jarvest, Richard L.; Boyd, Malcolm R.; Sutton, David; Vere Hodge, R. Anthony (Biosci. Res. Cent., Beecham Pharm. Res. Div., Epsom/Surrey, KT18 5XQ, UK). Journal of Medicinal Chemistry, 32(8), 1738-43 (English) **1989.** CODEN: JMCMAR. ISSN: 0022-2623. OTHER SOURCES: CASREACT 111:214873.

GI



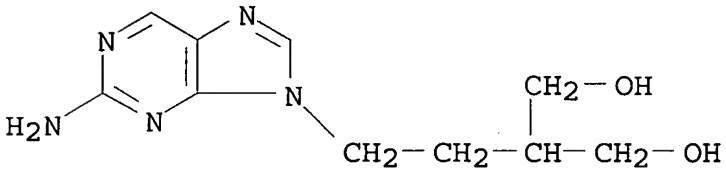
AB Potential oral prodrugs of the anitherpes virus acyclonucleoside 9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]guanine (I,BRL 39123) have been synthesized and evaluated for bioavailability of I in the blood of mice. Redn. of 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-amino-6-chloropurine with HCO2NH4-Pd afforded the 2-aminopurine II (R = Ac), which was hydrolyzed to the 5'-monoacetate and to 2-amino-9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]purine (II; R = H). II (R = H) was converted to addnl. monoester and diester derivs. and to its di-O-isopropylidene deriv. Both II (R = H) and its esters and isopropylidene deriv. were well adsorbed after oral administration and converted efficiently to I, II (R = Ac, EtCO) providing concns. of I in the blood that were >15-fold higher than those obsd. after dosing either I or its esters. Some previously prepd. 6-alkoxy-9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]purines also

showed improved absorption properties but their conversion to I was less efficient than that of the 2-aminopurine derivs. On the basis of these results and expts. involving detns. of rates of conversion to I in the presence of rat and human tissue prepns., II (R = Ac) (BRL 42810) was identified as the preferred prodrug of I. Oral bioavailability studies in healthy human subjects confirmed II (R = Ac) as an effective prodrug, and this compd. is being evaluated in clin. trials.

IT **104227-86-3P 104227-88-5P 104227-90-9P**
104227-93-2P 104227-94-3P 104227-97-6P
(prepn. of, prodrug of [hydroxy(hydroxymethyl)butyl]guanine)

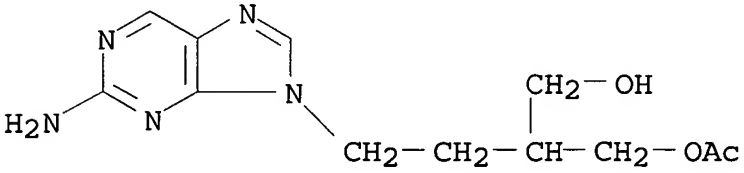
RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



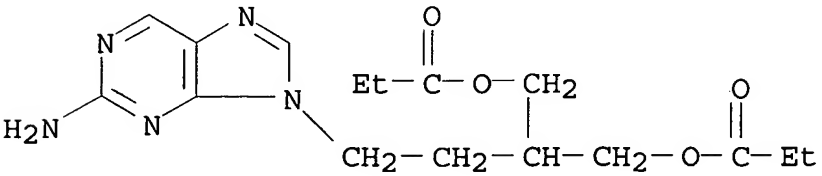
RN 104227-88-5 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monoacetate (ester) (9CI) (CA INDEX NAME)



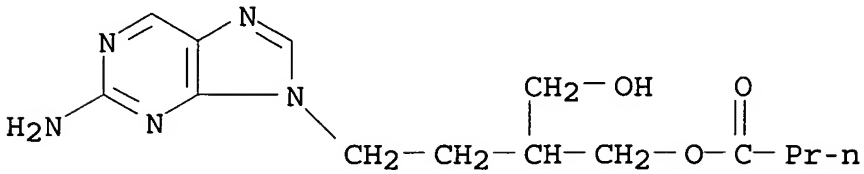
RN 104227-90-9 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, dipropanoate (ester) (9CI) (CA INDEX NAME)

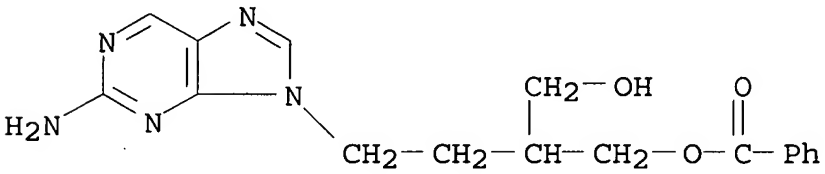


RN 104227-93-2 ZCAPLUS

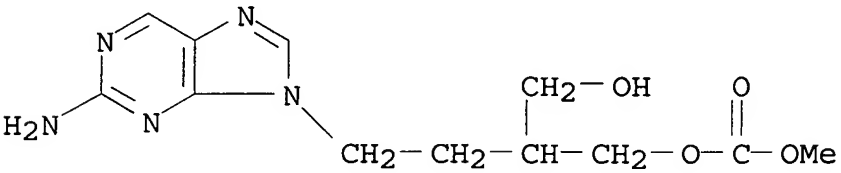
CN Butanoic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl ester (9CI) (CA INDEX NAME)



RN 104227-94-3 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monobenzoate (ester) (9CI) (CA INDEX NAME)



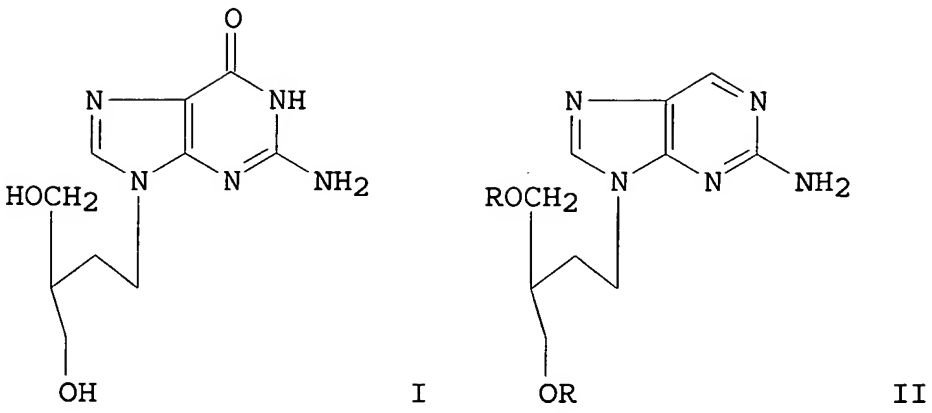
RN 104227-97-6 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl methyl ester (9CI) (CA INDEX NAME)



IT **104227-86-3P 104227-88-5P 104227-90-9P**
104227-93-2P 104227-94-3P 104227-97-6P
(prepn. of, prodrug of [hydroxy(hydroxymethyl)butyl]guanine)

L34 ANSWER 47 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1989:458254 Document No. 111:58254 Prodrugs of the selective antiherpesvirus agent 9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]guanine (BRL 39123) with improved gastrointestinal absorption properties. Harnden, Michael R.; Jarvest, Richard L.; Boyd, Malcolm R.; Sutton, David; Hodge, R. Anthony Vere (Biosci. Res. Cent., Beecham Pharm. Res. Div., Epsom/Surrey, KT18 5XQ, UK). Journal of Medicinal Chemistry, 32(8), 1738-43 (English) **1989.** CODEN: JMCMAR. ISSN: 0022-2623. OTHER SOURCES: CASREACT 111:58254.

GI

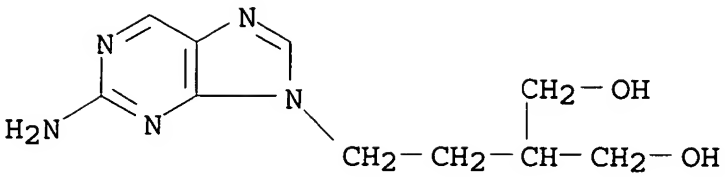


AB Potential oral prodrugs of the antiherpes virus acyclonucleoside 9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]guanine (I, BRL 39123) have been synthesized and evaluated for bioavailability of I in the blood of mice. Redn. of 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-amino-6-chloropurine with HCO2NH4-Pd afforded the 2-aminopurine II (R = Ac), which was hydrolyzed to the 5'-monoacetate and to 2-amino-9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]purine (II; R = H). II (R = H) was converted to addnl. monoester and diester derivs. and to its di-O-isopropylidene deriv. Both II (R = H) and its esters and isopropylidene deriv. were well adsorbed after oral administration and converted efficiently to I, II (R = Ac, EtCO) providing concns. of I in the blood that were >15-fold higher than those obsd. after dosing either I or its esters. Some previously prepd. 6-alkoxy-9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]purines also showed improved absorption properties, but their conversion to I was less efficient than that of the 2-aminopurine derivs. On the basis of these results and expts. involving detns. of rates of conversion to I in the presence of rat and human tissue prepns., II (R = Ac) (BRL 42810) was identified as the preferred prodrug of I. Oral bioavailability studies in healthy human subjects confirmed II (R = Ac) as an effective prodrug, and this compd. is being evaluated in clin. trials.

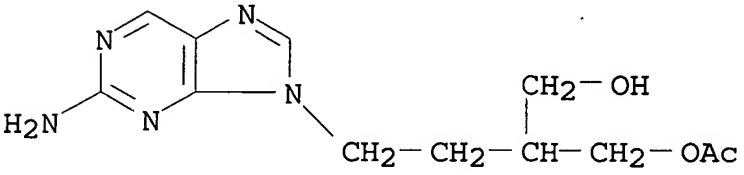
IT **104227-86-3P 104227-88-5P 104227-90-9P**
104227-93-2P 104227-94-3P 104227-97-6P
(prepn. of, prodrug of [hydroxy(hydroxymethyl)butyl]guanine)

RN 104227-86-3 ZCAPLUS

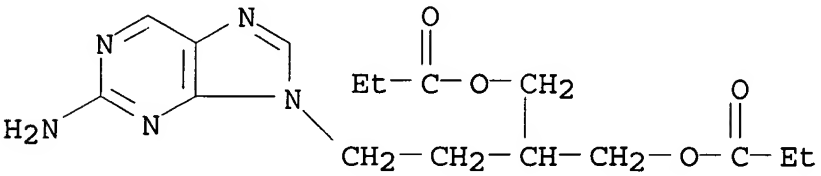
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



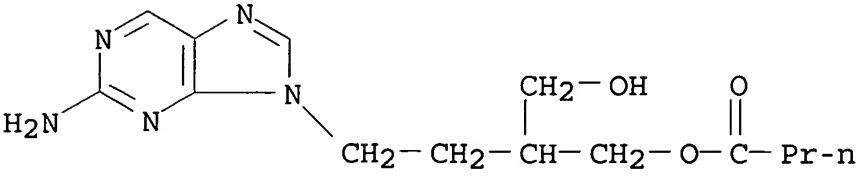
RN 104227-88-5 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monoacetate (ester) (9CI) (CA INDEX NAME)



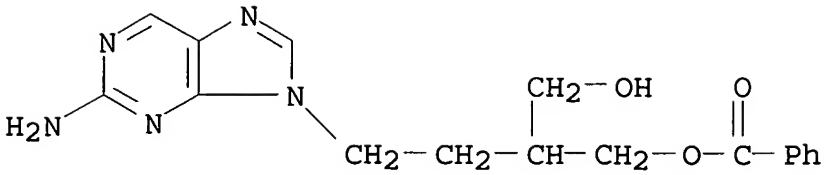
RN 104227-90-9 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, dipropanoate (ester) (9CI) (CA INDEX NAME)



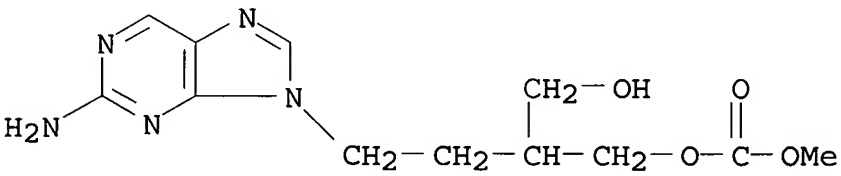
RN 104227-93-2 ZCAPLUS
CN Butanoic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl ester (9CI) (CA INDEX NAME)



RN 104227-94-3 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monobenzoate (ester) (9CI) (CA INDEX NAME)



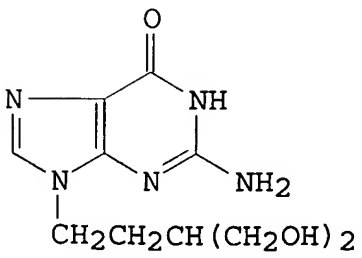
RN 104227-97-6 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl methyl ester (9CI) (CA INDEX NAME)



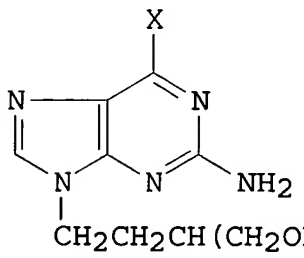
IT **104227-86-3P 104227-88-5P 104227-90-9P**
104227-93-2P 104227-94-3P 104227-97-6P
(prepn. of, prodrug of [hydroxy(hydroxymethyl)butyl]guanine)

L34 ANSWER 48 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1989:185958 Document No. 110:185958 Antiviral pharmaceuticals containing interferons and aminopurines. Cole, Martin; Boyd, Malcolm Richard; Sutton, David (Beecham Group PLC, UK). Eur. Pat. Appl. EP 271270 A2 **19880615**, 17 pp. DESIGNATED STATES: R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1987-310550 19871130. PRIORITY: GB 1986-28826 19861202.

GI



I



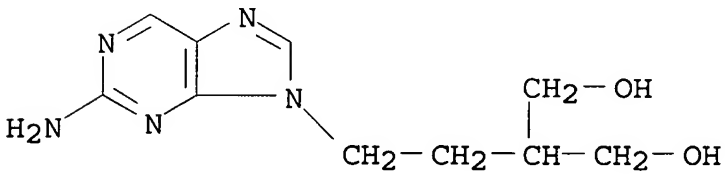
II

AB Antiviral pharmaceuticals contain: 1) an interferon and 2) purine I, its prodrugs II (X = H; R = H, Ac), or their pharmaceutically acceptable salts, phosphate esters, or acyl derivs. The IC50 of I against herpes simplex virus-1 was decreased from 0.34 to 0.01 .mu.g/mL by the addn. of 100 IU/mL of human .alpha.-interferon in vitro.

IT **104227-86-3**
(antiviral pharmaceuticals contg. interferons and)

RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)

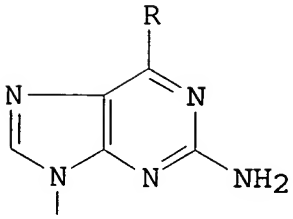


IT **104227-86-3**
(antiviral pharmaceuticals contg. interferons and)

L34 ANSWER 49 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN

1988:492663 Document No. 109:92663 Preparation of 2-aminopurines as precursors of a guanine virucide. Harnden, Michael Raymond; Jarvest, Richard Lewis (Beecham Group PLC, UK). PCT Int. Appl. WO 8705604 A1 **19870924**, 40 pp. DESIGNATED STATES: W: AT, FI, HU, KR, NO. (English). CODEN: PIXXD2. APPLICATION: WO 1986-GB153 19860317.

GI



I

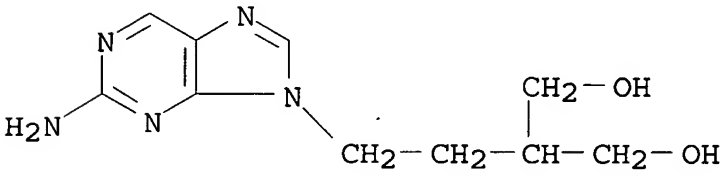
AB The title compds. I (R = H; R1, R2 = H, acyl, phosphoryl; R1R2 =

cyclic acetal, cyclic carbonate, cyclic phosphate) useful as virucides (no data) were prepd. by (a) hydrolysis of I in which R1R2 = Me2C; (b) hydrogenolysis of I in which R = Cl; (c) phosphorylating protected-amino I. I (R = Cl, R1R2 = Me2C) was refluxed in EtOH contg. Pd/C overnight to give I (R = R1 = R2 = H) which was stirred 16 h with (EtCO)2O in DMF contg. 4-(dimethylamino)pyridine to give I (R = H, R1 = R2 = COEt). The latter compd. gave a blood concn. of 20 .mu.g/mL 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine (II) in mice 15 min after oral gavage compared with 1.1 .mu.g II/mL 15 min after administration of II by itself.

IT **104227-86-3P 104227-88-5P 104227-90-9P**
104227-93-2P 104227-94-3P 104227-97-6P
(prepn. of, as guanine virucide precursor)

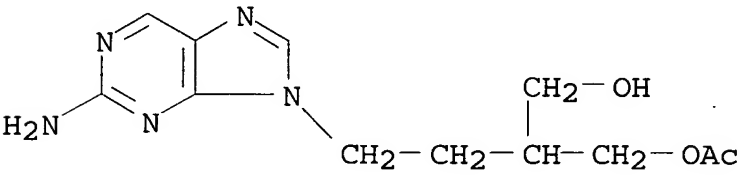
RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



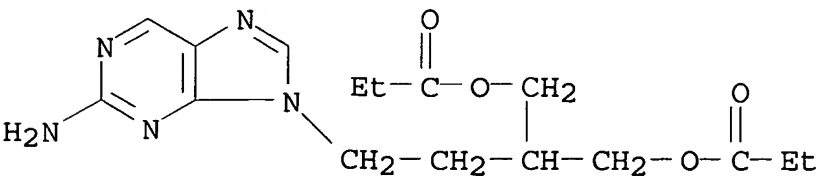
RN 104227-88-5 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monoacetate (ester) (9CI) (CA INDEX NAME)

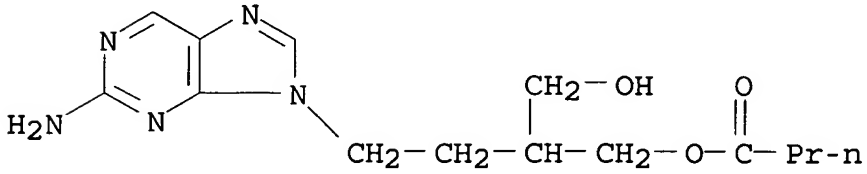


RN 104227-90-9 ZCAPLUS

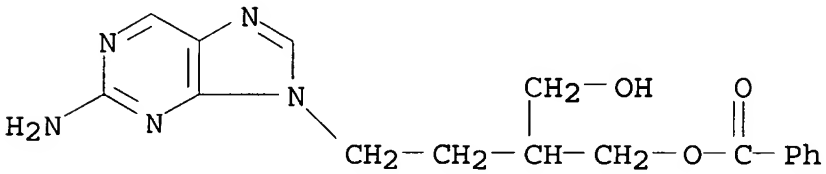
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, dipropanoate (ester) (9CI) (CA INDEX NAME)



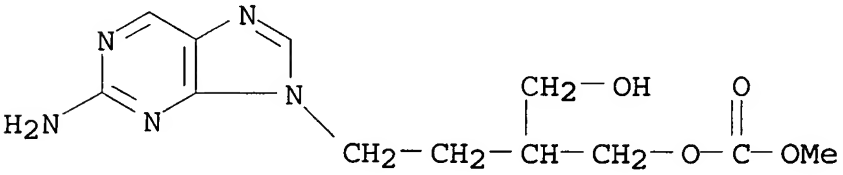
RN 104227-93-2 ZCAPLUS
CN Butanoic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl ester (9CI) (CA INDEX NAME)



RN 104227-94-3 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monobenzoate (ester) (9CI) (CA INDEX NAME)



RN 104227-97-6 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl methyl ester (9CI) (CA INDEX NAME)

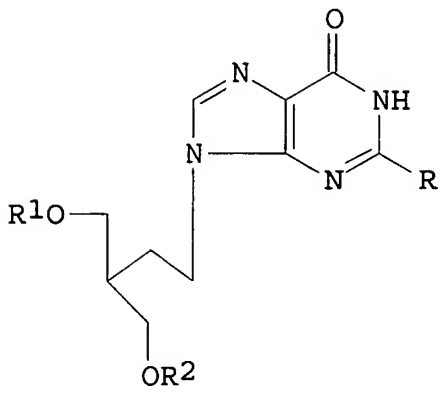


IT **104227-86-3P 104227-88-5P 104227-90-9P**
104227-93-2P 104227-94-3P 104227-97-6P
(prepn. of, as guanine virucide precursor)

L34 ANSWER 50 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1987:497051 Document No. 107:97051 Synthesis and antiviral activity of 9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]purines. Harnden, Michael R.; Jarvest, Richard L.; Bacon, Teresa H.; Boyd, Malcolm R. (Beecham Pharm. Res. Div., Biosci. Res. Cent., Epsom/Surrey, KT18 5XQ, UK). Journal of Medicinal Chemistry, 30(9), 1636-42 (English) **1987.** CODEN: JMCMAR. ISSN: 0022-2623. OTHER SOURCES:

CASREACT 107:97051.

GI



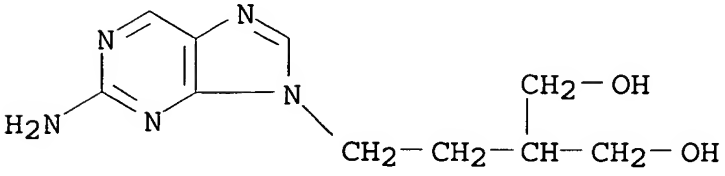
II

AB Alkylation of 2-amino-6-chloropurine with 5-(2-bromoethyl)-2,2-dimethyl-1,3-dioxane provided 2-amino-6-chloro-9-[2-(2,2-dimethyl-1,3-dioxan-5-yl)ethyl]purine (I) in high yield. I was readily converted to the antiviral acyclonucleoside II [R = NH2, R1 = R2 = H (III)] and to its 6-chloro, 6-thio, 6-alkoxy, 6-amino, and 6-deoxy purine analogs. III was also converted to its xanthine analog. Similarly, alkylation of 6-chloropurine provided a route to II (R = R1 = R2 = H).. Of these 9-substituted purines, III showed the highest activity against herpes simplex virus types 1 and 2 in cell cultures, and in some tests it was more active than acyclovir, with no evidence of toxicity for the cells. A series of monoesters and diesters of III were prepd., and some of these also showed antiherpes virus activity in cell cultures, the most active ester being the dihexanoate II [R = NH2, R1 = R2 = Me(CH2)4CO].

IT **104227-86-3P**
(prepn. of)

RN 104227-86-3 ZCAPLUS

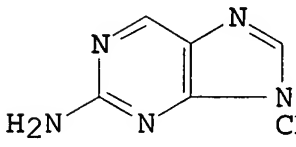
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



IT **104227-86-3P**
(prepn. of)

L34 ANSWER 51 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1986:552836 Document No. 105:152836 Purine derivatives and a pharmaceutical preparation. Johansson, Karl Nils Gunnar; Kovacs, Zsuzsanna Maria Ilona; Lindborg, Bjoern Gunnar; Stening, Goeran Bertil (Astra Laekemedel AB, Swed.). Eur. Pat. Appl. EP 186640 A1 **19860702**, 52 pp. DESIGNATED STATES: R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1985-850398 19851213. PRIORITY: SE 1984-6538 19841221.

GI

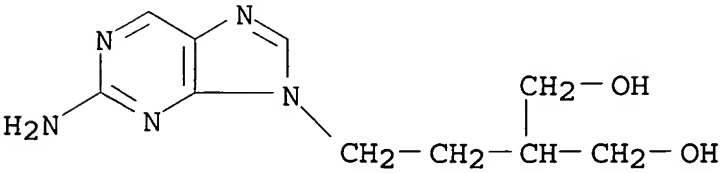


H_2N $CH_2CHR^1CR^2R^3CH_2OH$ I

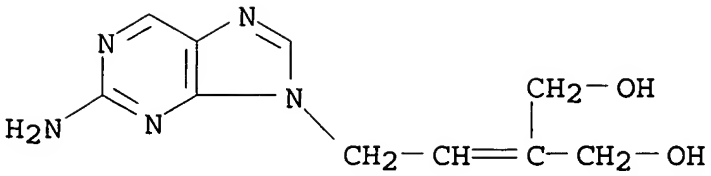
AB The title compds. I (R1 = OH, HOCH2; R2 = H, OH, HOCH2; R3 = H; or R2R3 = C-C bond) and their salts, useful for treatment of virus infections, were prepd. Thus, (R)-4-(2-amino-6-chloropurin-9-yl)-O1,O2-isopropylidenebutane-1,2-diol was dechlorinated to give the amino deriv., which was deprotected to give (R)-I (R1 = R3 = H; R2 = OH) (II). The antiviral effect of II at 15 mg/kg was demonstrated in mice infected with herpes simplex type 2 virus. A tablet formulation contained I 20 mg and common adjuvants to 250 mg.

IT **104227-86-3P 104618-59-9P 104618-61-3P**
(prepn. of, as antiviral agent)

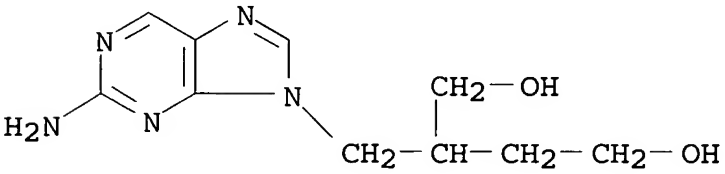
RN 104227-86-3 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



RN 104618-59-9 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethylidene]- (9CI) (CA INDEX NAME)

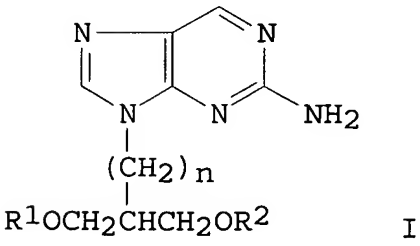


RN 104618-61-3 ZCAPLUS
CN 1,4-Butanediol, 2-[(2-amino-9H-purin-9-yl)methyl]- (9CI) (CA INDEX NAME)



IT **104227-86-3P 104618-59-9P 104618-61-3P**
(prepn. of, as antiviral agent)

L34 ANSWER 52 OF 52 ZCAPLUS COPYRIGHT 2006 ACS on STN
1986:533669 Document No. 105:133669 Aminopurine derivatives. (Beecham Group PLC, UK). Jpn. Kokai Tokkyo Koho JP 61085388 A2 **19860430** Showa, 14 pp. (Japanese). CODEN: JKXXAF.
APPLICATION: JP 1985-207693 19850919. PRIORITY: GB 1984-23833 19840920; GB 1985-10331 19850423; GB 1985-20618 19850816.
GI



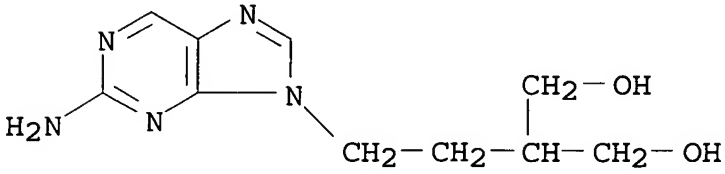
I

AB Title compds. I (R1, R2 = H, acyl, phosphate, etc.) and their salts, useful as virucides (no data), were prepd. Thus, refluxing 0.54 g 2-amino-6-chloro-9-chloro-9-[2-(2,2-dimethyl-1,3-dioxan-3-yl)ethyl]purine with 450 mg 10% Pd/C in ethanol and cyclohexane gave 36% 2-amino-9-[4-hydroxy-3-(hydroxymethyl)-but-1-yl]purine.
IT **104227-86-3P 104227-88-5P 104227-90-9P**
104227-93-2P 104227-94-3P 104227-97-6P

(prepn. of, as virucide)

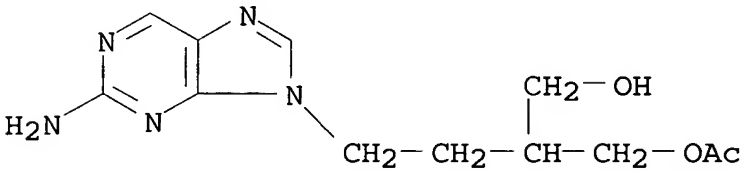
RN 104227-86-3 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]- (9CI) (CA INDEX NAME)



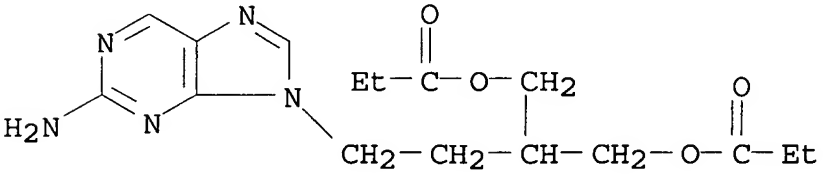
RN 104227-88-5 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monoacetate (ester) (9CI) (CA INDEX NAME)



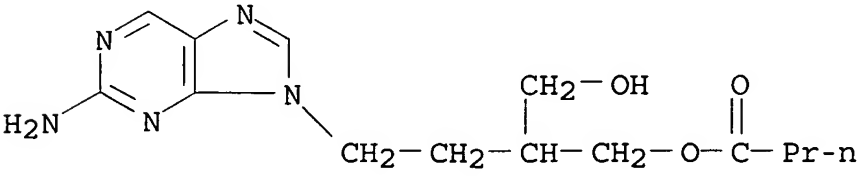
RN 104227-90-9 ZCAPLUS

CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, dipropanoate (ester) (9CI) (CA INDEX NAME)

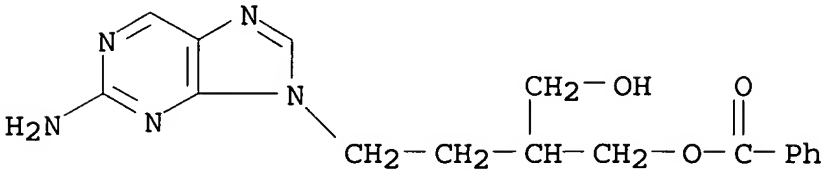


RN 104227-93-2 ZCAPLUS

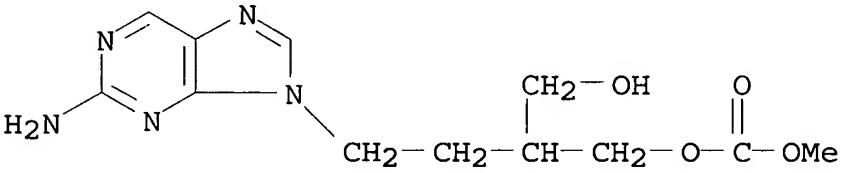
CN Butanoic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl ester (9CI) (CA INDEX NAME)



RN 104227-94-3 ZCAPLUS
CN 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, monobenzoate (ester) (9CI) (CA INDEX NAME)



RN 104227-97-6 ZCAPLUS
CN Carbonic acid, 4-(2-amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl methyl ester (9CI) (CA INDEX NAME)



IT **104227-86-3P 104227-88-5P 104227-90-9P**
104227-93-2P 104227-94-3P 104227-97-6P
(prepn. of, as virucide)